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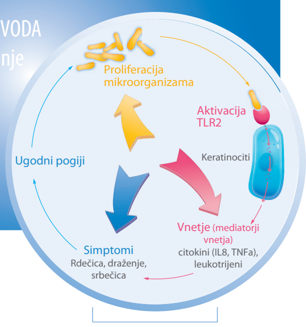

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Srbečica	- 88%
Otroci**	
Temenice	- 79%

*Klinična raziskava z DS emulzijo tekom 4 tednov

** Klinična raziskava z DS emulzijo tekom 4 tednov, testirano na otrocih s temenicami

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Syphilis and HIV co-infection: excellent response to multiple doses of benzathine penicillin

Andreja Saje[1] ✉, Janez Tomažič[2]

Abstract

Background: The number of new syphilis diagnoses in Slovenia is steadily increasing, especially among HIV-infected men who have sex with men (MSM). We studied the effect of penicillin for treating syphilis in HIV co-infected patients and risk factors for treatment failure. The primary endpoint was response to therapy (fourfold reduction of VDRL at month 12).
Methods: Three hundred forty-two paper records were reviewed and MSM with positive VDRL and/or TPHA and serological follow up of at least 12 months were enrolled in the survey.
Results: Incidence of syphilis increased from 1.2% (2005) and 2.9% (2007) to 6.4% (2009) and 3.8% (2011, until July). Two hundred sixty-one (76.3%) were MSM and 102 (29.8%) were co-infected; 53.9% had primary/secondary syphilis, 37.3% latent syphilis, and 8.8% neurosyphilis. Patients with primary/secondary/latent syphilis were treated with three doses of benzathine penicillin (2.4 MU i.m.). Treatment was successful in 92.2%. With respect to risk factors, there was no difference between the "success" and "failure" group. Twenty-six patients (25.5%) had re-infections.
Conclusions: The rate of cure in our study population was excellent, probably due to a low degree of immunosuppression and a three-dose benzathine penicillin regimen.

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Introduction

Syphilis and HIV infection have been observed to facilitate the acquisition of one another and are in epidemiological synergy (1, 2). In recent years, the incidence of syphilis among men who have sex with men (MSM) has increased rapidly, especially among HIV-infected MSM (3–8). This has been attributed to an increase in sexual risk behavior (9–11) and to decreased mortality associated with Highly Active Antiretroviral Therapy (HAART) (12, 13).

HIV co-infected patients may experience more syphilis treatment failure than patients with syphilis mono-infection (14). However there is little information about factors influencing syphilis treatment failure in HIV co-infected patients. The aim of our nationwide study was to analyze the effect of penicillin for treating syphilis in HIV co-infected patients and risk factors for treatment failure among adult HIV-positive individuals in Slovenia. The primary endpoint was response to therapy; a fourfold reduction of VDRL titers at month 12 after treatment was considered to be adequate.

Methods

This study was approved by the National Medical Ethics Committee of the Republic of Slovenia (NMEC).

Study group

Three hundred forty-two paper records of adult HIV-infected patients were reviewed. In Slovenia, VDRL and TPHA titers are used for primary screening, and patients with positive tests and no prior treatment are considered to have newly diagnosed syphilis. MSM patients with positive VDRL and/or TPHA tests and serological follow up of at least 12 months were enrolled in the survey. All patients with primary/secondary/latent syphilis were treated with three doses of benzathine penicillin (2.4 MU, i.m.).

Variables

We collected data on demographics, route of transmission, co-infections with hepatitis B or C, smoking, parameters of the immune status (viral load (VL), CD4 T cell counts, stage of HIV infection according to the Centers for Disease Control and Prevention (CDC stage), and treatment with HAART), and stage of syphilis at diagnosis. Serologic data (VDRL/RPR, TPHA, and FTA IgG tests) at diagnosis and during follow-up (6, 12, and 24 months after treatment) were also obtained. VDRL/RPR titers were assessed and categorized into "success" (fourfold decrease in VDRL/RPR titers at month 12 after treatment) and "failure" (no fourfold decrease in VDRL/RPR titers 12 months after treatment). VL was evaluated as a dichotomous variable (≥ 40 copies/mL or < 40 copies/mL). Treatment with HAART was evaluated as affirmative if the patient had been treated for at least 6 months; otherwise it was evaluated as negative.

Statistical analysis

For analysis, descriptive statistics with the chi square test, Mann–Whitney test, Kruskal–Wallis test, and logistic regression were used, using SPSS 21.0 (SPSS, Chicago, IL, USA). Using logistic regression, we assessed associations between syphilis treatment failure and the following outcomes: treatment with HAART, smoking, and CDC stage C. $P < 0.05$ was considered statistically significant. From this analysis we excluded patients that had negative VDRL/RPR titers at the beginning of follow-up at our Clinic for Infectious Diseases and Febrile Illnesses (n = 17) and patients without follow-up 12 months after treatment of syphilis (n = 8) because we could not assess the success of syphilis treatment.

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Results

The first patient in Slovenia with syphilis and HIV co-infection was diagnosed in 1987. Before 2005 we found only six additional cases. After that, the incidence of syphilis among our HIV-positive population increased progressively from four (1.2%) cases (2005) and 10 (2.9%) cases (2007) to 22 (6.4%) cases (2009) and 13 (3.8%) cases (first half of 2011). Out of 342 HIV-infected patients, 261 (76.3%) were MSM and 102 (29.8%) also had syphilis; of these, 40.2% (n = 41) were diagnosed simultaneously, 50.0% (n = 51) had a new diagnosis of syphilis, and 9.8% (n = 10) had a prior infection. The average age of our patients was 40.9 years; median per-patient follow-up was 5 years.

Fifty-five patients (53.9%) had primary/secondary syphilis, 38 patients (37.3%) had latent syphilis, and nine patients (8.8%) had neurosyphilis. Patients with primary/secondary/latent syphilis were treated with three doses of benzathine penicillin (2.4 million units, i.m.). Seventy-seven patients (89.6%) had a fourfold decrease in VDRL/RPR test 12 months after treatment (successful treatment). Including those that were excluded from statistical analysis (studying risk factors for treatment failure), the treatment was successful in 92.2% (n = 94). The initial average CD4 T cell count was 427 cells/mL. Out of 102 patients, 26 (25.5%) had re-infections. According to statistical analysis, there was no significant difference between the "success" and "treatment failure" group ($p > 0.05$) (Table 1).

Multiple logistic regression included the factors HAART treatment, CDC stage, and smoking. None of them were significantly associated with treatment failure of syphilis ($p > 0.05$) (Table 2).

Table 1 | **Characteristics of HIV and syphilis co-infected patients according to treatment response (n = 77)*. SD – standard deviation; HBV/HCV + – Infected with the virus of hepatitis B and/or hepatitis C; CDC – Centers for Disease Control and Prevention (Atlanta, GA, USA); CD4 – CD4 T cell count at the time of the diagnosis and treatment of syphilis; VL – HIV viral load at the time of the diagnosis and treatment of syphilis (number of copies of HIV-RNA/1 mL); HAART treatment – treatment with Highly Active Antiretroviral Therapy for a minimum of 6 months; re-infected – with a fourfold increase of VDRL / RPR test after successful treatment of syphilis.**

Protocols	Treatment success after 12 months	Treatment failure after 12 months	P value
N of patients (%)	69 (89.6)	8 (10.4)	
Age (± SD)	40.75 (± 10.91)	41.25 (± 10.96)	0.682
Slovenians (%)	64 (92.8)	7 (87.5)	0.557
Smokers (%)	22 (44.9)	5 (83.3)	0.196
HBV/HCV + (%)	3 (4.3)	1 (12.5)	0.366
CDC stage C (%)	19 (27.9)	3 (37.5)	0.107
CD4 (± SD)	450.9 (± 308.6)	338.4 (± 250.9)	0.423
VL ≥ 40 copies/mL (%)	42 (61.8)	5 (62.5)	0.166
HAART treatment (%)	24 (34.8)	1 (12.5)	0.203
Syphilis stage	/	/	0.61
Primary/secondary (%)	45 (65.2)	2 (25.0)	
Latent (%)	19 (27.5)	4 (50.0)	
Neurosyphilis (%)	5 (7.3)	2 (25.0)	
VDRL/RPR at diagnosis (median)	64.0	48.0	0.679
TPHA at diagnosis (median)	2,560.0	3,200.0	0.827
IgG at diagnosis	1,280.0	2,560.0	0.627
Re-infected (%)	20 (29.0)	4 (50.0)	0.224

*Note that we studied treatment success in 102 patients, but only 77 were included in the presented statistical analysis for evaluating risk factors for treatment failure.

Discussion

Since the early 2000s, for the first time since the introduction of HAART, the number of newly diagnosed HIV infections in the developed world has increased considerably compared to previous years. The increase was largely restricted to MSM from larger cities. This has been attributed to a decrease in safe sex practices. Simultaneously the re-emergence of syphilis, especially among MSM, was observed worldwide and a significant proportion of patients have been found to be co-infected with HIV (3, 5, 6).

We found a significant rise in the incidence of syphilis in the Slovenian HIV-positive MSM population after 2004. By 2011, 29.8% of all HIV-positive patients had had syphilis. The majority (76.3%) of the HIV-positive population in our study are MSM. A recent Slovenian study has shown a deterioration of safe sexual behavior among MSM and sexual mixing among Slovenian MSM and MSM abroad (15). Sexual risk taking goes on after the diagnosis of HIV and/or syphilis in a sizeable proportion of our MSM population, a result of which is probably also the high rate of re-infections in our study (25.5%). This suggests that implementing more strenuous safe-sex education may be effective in lowering the HIV and syphilis burden, as stated in some studies (16, 17). The rate of successfully treated individuals in our cohort was surprisingly good, which was most probably due to the low degree of immunosuppression and more intensive treatment regimen for early syphilis. The latter has already been advised by some authors (18–20). According to statistical analysis of different variables, there was no significant difference between the "success" and "treatment failure" group ($p > 0.05$). Similar findings are reported in many similar studies with patients mostly receiving HAART treatment and with an intact immune system (21–25). In Slovenia, HIV-positive patients start their HAART regimen treatment immediately after HIV diagnosis. In our study we included in the group "treated with HAART" only patients that had been treated with HAART for at least 6 months. Many patients were diagnosed with syphilis and HIV coincidentally or syphilis preceded HIV diagnosis, which gives a false low estimation of the rate of HAART treated. According to the statistical analysis, there was also no association between syphilis stage and values of serological tests 12 months after treatment ($p > 0.05$). This differs from the results of other studies. Some studies found that an increased treatment failure rate among the HIV-positive population was connected with early syphilis stage (primary and/or secondary and/or early latent syphilis) (26–28).

An important strength of our study is the total coverage of patients with double infection due to the fact that all Slovenian HIV-positive patients are screened, treated, and followed up at one center. However, due to the small number of participants in some study groups, statistical analysis may have yielded unreliable results.

Our findings may serve to guide clinicians to intensify the treatment and follow-up of HIV-infected patients with syphilis because of the possibility of re-infection.

Table 2 | **Multiple logistic regression of factors influencing treatment failure of syphilis. HAART treatment – treatment with Highly Active Antiretroviral Therapy for minimum of 6 months; CDC – Centers for Disease Control and Prevention (Atlanta, GA, USA).**

Factor	Observed category	Reference category	Odds ratio	95% confidence interval	P value
HAART treatment	Yes	No	0.720	0.048–10.873	0.812
CDC stage	C	Non C	3.034	0.357–25.759	0.309
Smoking	Yes	No	4.007	0.276–58.168	0.309

References

1. Rottingen JA, Cameron WD, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? Sexually Transmitted Diseases. 2001;28:579-97.
2. Wasserheit JN. Epidemiological synergy: interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. Sexually Transmitted Diseases. 1992;19:61-77.
3. Ashton M, Sopwith W, Clark P, McKelvey D, Lighton L, Mandal D. An outbreak no longer: factors contributing to the return of syphilis in Greater Manchester. Sexually Transmitted Infections. 2003;79:291-3.
4. Heffelfinger JD, Swint EB, Berman SM, Weinstock HS. Trends in primary and secondary syphilis among men who have sex with men in the United States. American Journal of Public Health. 2007;97:1076-83.
5. Jakopanec I, Grjibovski AM, Nilsen O, Aavitsland P. Syphilis epidemiology in Norway, 1992–2008: resurgence among men who have sex with men. BMC Infectious Diseases. 2010;10:105.
6. Marcus U, Kollan C, Bremer V, Hamouda O. Relation between the HIV and the re-emerging syphilis epidemic among MSM in Germany: an analysis based on anonymous surveillance data. Sexually Transmitted Infections. 2005;81:456-7.
7. Peterman TA, Furness BW. The resurgence of syphilis among men who have sex with men. Current Opinion in Infectious Diseases. 2007;20:54-9.
8. Spielmann N, Munstermann D, Hagedorn HJ, An der Heiden M, Houareau C, Gunsenheimer-Bartmeyer B, et al. Time trends of syphilis and HSV-2 co-infection among men who have sex with men in the German HIV-1 seroconverter cohort from 1996–2007. Sexually Transmitted Infections. 2010;86:331-6.
9. Nakamura N, Mausbach BT, Ulibarri MD, Semple SJ, Patterson TL. Methamphetamine use, attitudes about condoms, and sexual risk behavior among HIV-positive men who have sex with men. Archives of Sexual Behavior. 2011;40:267-72.
10. van Kesteren NM, Hospers HJ, Kok G. Sexual risk behavior among HIV-positive men who have sex with men: a literature review. Patient Education and Counseling. 2007;65:5-20.
11. Stolte IG, Dukers NH, Geskus RB, Coutinho RA, de Wit JB. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. AIDS. 2004;18:303-9.
12. Ostrow DE, Fox KJ, Chmiel JS, Silvestre A, Visscher BR, Vanable PA, et al. Attitudes towards highly active antiretroviral therapy are associated with sexual risk taking among HIV-infected and uninfected homosexual men. AIDS. 2002;16:775-80.
13. Stolte IG, Dukers NHTM, De Wit JBF, Fennema JSA, Coutinho RA. Increase in sexually transmitted infections among homosexual men in Amsterdam in relation to HAART. Sexually Transmitted Infections. 2001;77:184-6.
14. Ghanem KG, Erbelding EJ, Wiener ZS, Rompalo AM. Serological response to syphilis treatment in HIV-positive and HIV-negative patients attending sexually transmitted diseases clinics. Sexually Transmitted Infections. 2007;83:97-101.
15. Klavs I, Bergant N, Kastelic Z, Lamut A, Kustec T. Disproportionate and increasing burden of HIV infection among men who have sex with men in Slovenia: surveillance data for 1999–2008. Euro Surveill. 2009;14(47):pii=19419. [Internet]. Stockholm (Sweden): European Centre for Disease Prevention and Control. c2007–2013 - [Cited 2013 Oct 20]. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19419.
16. Boyer CB, Sieverding J, Siller J, Gallaread A, Chang YJ. Youth United Through Health Education: community-level, peer-led outreach to increase awareness and improve noninvasive sexually transmitted infection screening in urban African American youth. Journal of Adolescent Health. 2007;40:499-505.
17. Xu JJ, Reilly KH, Lu CM, Ma N, Zhang M, Chu ZX, et al. A cross-sectional study of HIV and syphilis infections among male students who have sex with men (MSM) in northeast China: implications for implementing HIV screening and intervention programs. BMC Public Health. 2011;11:287.
18. Bordon J, Martinez-Vazquez C, De La Fuente-Aguado J, Sopena B, Ocampo-Hermida A, Nunez-Torron J, et al. Response to standard syphilis treatment in patients infected with the human immunodeficiency virus. European Journal of Clinical Microbiology and Infectious Diseases. 1999;18:729-32.
19. Nandwani R, Fisher M. Clinical standards for the screening and management of acquired syphilis in HIV-positive adults. International Journal of STD and AIDS. 2006;17:588-93.
20. Yinnon AM, Coury-Doniger P, Polito R, Reichman RC. Serologic response to treatment of syphilis in patients with HIV infection. Archives of Internal Medicine. 1996;156:321-5.
21. Long CM, Klausner JD, Leon S, Jones FR, Giron M, Cuadros J, et al. Syphilis treatment and HIV infection in a population-based study of persons at high risk for sexually transmitted disease / HIV infection in Lima, Peru. Sexually Transmitted Diseases. 2006;33:151-5.
22. Manavi K, McMillan A. The outcome of treatment of early latent syphilis and syphilis with undetermined duration in HIV-infected and HIV-uninfected patients. International Journal of STD & AIDS. 2007;18:814-8.
23. Riedner G, Rusizoka M, Todd J, Maboko L, Hoelscher M, Mmbando D, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. New England Journal of Medicine. 2005;353:1236-44.
24. Farhi D, Benhaddou N, Grange P, Zizi N, Deleuze J, Morini JP, et al. Clinical and serologic baseline and follow-up features of syphilis according to HIV status in the post-HAART era. Medicine. 2009;88:331-40.
25. Kingston MA, Higgins SP. Comparison of the serological response to treatment of early syphilis in HIV positive versus HIV negative individuals [3]. Sexually Transmitted Infections. 2004;80:152-3.
26. Kim JH, Psevdos G, Jr., Suh J, Sharp V. Factors influencing syphilis treatment failure and/or re-infection in HIV co-infected patients: immunosuppression or behaviors. Chinese Medical Journal. 2011;124:2123-6.
27. Rolfs RT, Joesoef MR, Hendershot EF, Rompalo AM, Augenbraun MH, Chiu M, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. New England Journal of Medicine. 1997;337:307-14.
28. Telzak EE, Greenberg MS, Harrison J, Stoneburner RL, Schultz S. Syphilis treatment response in HIV-infected individuals. AIDS. 1991;5:591-5.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA. Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila, ki ga dobite pri naših strokovnih sodelavcih ali na sedežu družbe Merck Sharp & Dohme! SESTAVA: Ena viala vsebuje 100 mg infliksimaba. Infliksimab je himerno človeško–mišje monoklonsko protitelo IG1 pridobljeno v mišjih hibridoma celicah s tehnologijo rekombinantne DNK. Po rekonstituciji vsebuje en mililiter 10 mg infliksimaba. **INDIKACIJE:** (i) V kombinaciji z metotreksatom za zmanjšanje znakov in simptomov revmatoidnega artritisa ter izboljšanje funkcije sklepov pri odraslih bolnikih z aktivno boleznijo, kadar odziv na protirevmatična zdravila, ki vplivajo na imunsko odzivnost, vključno z metotreksatom, ni zadosten; in pri odraslih bolnikih s hudo, aktivno in progresivno boleznijo, ki še niso bili zdravljeni z metotreksatom ali drugimi protirevmatičnimi zdravili. (ii) Zdravljenje zmerno do močno aktivne Crohnove bolezni pri odraslih bolnikih, ki se niso odzvali na celoten in ustrezen ciklus zdravljenja s kortikosteroidom in/ali zdravilom za zaviranje imunske odzivnosti, ali pri tistih, ki ne prenašajo tovrstne terapije ali ki imajo medicinske kontraindikacije zanjo; zdravljenje aktivne Crohnove bolezni s fistulami pri odraslih bolnikih, ki se niso odzvali na celoten in ustrezen ciklus konvencionalnega zdravljenja. (iii) Zdravljenje hude, aktivne Crohnove bolezni pri otrocih in mladostnikih, starih od 6 do 17 let, ki se niso odzvali na običajno terapijo, ter pri tistih, ki ne prenašajo teh običajnih načinov zdravljenja oziroma imajo kontraindikacije zanje. (iv) Zdravljenje zmerno do močno aktivnega ulceroznega kolitisa pri odraslih bolnikih, ki so se nezadostno odzvali na običajno zdravljenje, ter pri tistih, ki ne prenašajo takšnega zdravljenja ali imajo medicinske kontraindikacije zanj. (v) Zdravljenje močno aktivnega ulceroznega kolitisa pri pediatričnih bolnikih, starih od 6 do 17 let, ki so se nezadostno odzvali na običajno zdravljenje, na primer na kortikosteroide in 6-MP ali AZA, ter pri tistih, ki ne prenašajo takšnega zdravljenja ali imajo medicinske kontraindikacije zanj. (vi) Zdravljenje hudega aktivnega ankilozirajočega spondilitisa pri odraslih bolnikih, ki so se nezadostno odzvali na konvencionalno terapijo. (vii) Zdravljenje aktivnega in napredujočega psoriatičnega artritisa pri odraslih bolnikih v primeru nezadostnega odziva na predhodno zdravljenje s protirevmatičnimi zdravili DMARD v kombinaciji z metotreksatom ali samostojno pri bolnikih, ki ne prenašajo metotreksata ali pri katerih je metotreksat kontraindiciran. (viii) Zdravljenje zmerne do hude psoriaze s plaki pri odraslih bolnikih, ki se niso odzvali na druge sistemske terapije ali pa imajo kontraindikacijo zanje ali jih ne prenašajo. **ODMERJANJE IN NAČIN UPORABE:** Revmatoidni artritis: Odmerek je 3 mg/kg v intravenski infuziji v času 2 ur. Temu naj sledita dodatni infuziji z odmerkoma 3 mg/kg, 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Če se bolnik nezadostno odzove na zdravilo ali če pri njem odziv pozneje izgine, mu lahko tudi postopoma povečujete odmerek za približno 1,5 mg/kg na vsakih 8 tednov, do največ 7,5 mg/kg. Druga možnost pa je, da bolniku daste 3 mg/kg že na vsake 4 tedne. Zmerno do močno aktivna Crohnova bolezen: Odmerek je 5 mg/kg v intravenski infuziji v času 2 ur, temu pa naj sledita še dodatni infuziji zdravila v odmerku 5 mg/kg v 2. tednu po prvi infuziji. Če se bolnik ne odzove na zdravljenje po 2 odmerkih zdravila, mu ne smete več dajati infliksimaba. Pri bolnikih, ki so se odzvali na zdravilo, so druge možnosti nadaljnjega zdravljenja naslednje: Vzdrževalno zdravljenje: Dodatni infuziji v odmerku 5 mg/kg 6 tednov po prvem odmerku, čemur naj sledijo infuzije na vsakih 8 tednov, ali ponovno dajanje zdravila: Infuzija odmerka 5 mg/kg, če se ponovijo znaki in simptomi bolezni. Aktivna Crohnova bolezen s fistulami: Intravenski infuziji 5 mg/kg v času 2 ur naj sledita dodatni infuziji 5 mg/kg 2 in 6 tednov po prvi infuziji. Pri bolnikih, ki se odzovejo na zdravilo, so možnosti nadaljnjega zdravljenja naslednje: Vzdrževanje: Dodatne infuzije z odmerkom 5 mg/kg na vsakih 8 tednov, ali ponovno dajanje: Infuzija 5 mg/kg zdravila, če se ponovijo znaki in simptomi bolezni, čemur naj sledijo infuzije z odmerkom 5 mg/kg na vsakih 8 tednov. Ulcerozni kolitis: Odmerek je 5 mg/kg v obliki intravenske infuzije, ki naj traja 2 uri. Temu naj sledita dva dodatna infuzijska odmerka po 5 mg/kg v 2. in 6. tednu po prvi infuziji, potem pa zdravilo infundirajte bolniku na vsakih 8 tednov. Ankilozirajoči spondilitis: Odmerek je 5 mg/kg v intravenski infuziji v času 2 ur, čemur naj sledita dodatni infuziji z odmerkoma 5 mg/kg 2 in 6 tednov po prvi infuziji, potem pa na vsakih 6 do 8 tednov. Psoriatični artritis: Odmerek je 5 mg/kg v intravenski infuziji v času 2 ur, čemur naj sledita dodatni infuziji z odmerkoma 5 mg/kg 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Psoriaza: 5 mg/kg, dano v obliki 2 urne intravenske infuzije, potem pa dodatne infuzije odmerkov 5 mg/kg 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Ponovna uporaba zdravila za vse indikacije: V primeru prekinitve vzdrževalnega zdravljenja, in potrebe po ponovni uvedbi zdravljenja, ni priporočljiva ponovna uporaba uvodne sheme. V tem primeru bolniku najprej ponovno uvedite zdravilo Remicade v enkratnem odmerku, pozneje pa mu spet predpišite vzdrževalni odmerek zdravila v skladu s priporočili, ki so podana zgoraj. Crohnova bolezen (pri bolnikih, starih od 6 do 17 let): Običajen odmerek je 5 mg/kg. Bolniku ga dajte v obliki 2 urne intravenske infuzije, ki naj ji sledita še dve infuziji v istem odmerku, in sicer 2 in 6 tednov po prvi infuziji, potem pa nadaljujte z infuzijami za vzdrževalno zdravljenje na vsakih 8 tednov. Ulcerozni kolitis (od 6 do 17 let): Odmerek je 5 mg/kg v intravenski infuziji, ki traja 2 uri. Temu naj sledita dodatni infuziji z odmerkom 5 mg/kg 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Skrajšane infuzije pri indikacijah za odrasle bolnike: Pri skrbno izbranih bolnikih, ki so dobro prenesli vsaj 3 začetne 2-urne infuzije zdravila Remicade in so trenutno na vzdrževalnem zdravljenju, lahko razmislite o skrajšanju naslednjih infuzij, vendar ne na manj kot 1 uro. Če pri skrajšani infuziji nastopi z njo povezana reakcija in je treba zdravljenje nadaljevati, lahko pri naslednjih infuzijah razmislite o uporabi manjše hitrosti infundiranja. Uporabe skrajšanih infuzij v odmerkih > 6 mg/kg niso proučevali. **KONTRAINDIKACIJE:** Bolniki z anamnezo preobčutljivosti na infliksimab, druge mišje beljakovine ali katero od pomožnih snovi. Bolniki s tuberkulozo ali z drugimi hudimi okužbami, kakor so npr. sepsa, abscesi in oportunistične okužbe. Bolniki z zmernim do hudim srčnim popuščanjem (razred III/IV po NYHA). **POVZETEK POSEBNIH OPOZORIL, PREVIDNOSTNIH UKREPOV IN INTERAKCIJ:** Zdravljenje z infliksimabom je bilo povezano z akutnimi infuzijskimi reakcijami, vključno z anafilaktičnim šokom in poznimi preobčutljivostnimi reakcijami. Če se pojavi akutna infuzijska reakcija, morate infuzijo takoj prekiniti. Na voljo morajo biti sredstva za nujno pomoč. Za preprečevanje blagih in prehodnih učinkov lahko bolnikom pred zdravljenjem z zdravilom Remicade daste premedikacijo. Če se pojavijo resne reakcije, morate uvesti simptomatično zdravljenje in bolniku ne smete več dajati infuzij tega zdravila. Če bolnik po daljšem obdobju ponovno prejme zdravilo Remicade, ga morate skrbno spremljati zaradi morebitnega pojava znakov in simptomov pozne preobčutljivosti. Pred, med in po zdravljenju z zdravilom Remicade morate bolnike skrbno spremljati, da ugotovite morebitne okužbe, npr. tuberkulozo. Bolnika ne smete več zdraviti s tem zdravilom, če dobi resno okužbo ali sepso. Zaviranje TNFα lahko prikrije simptome okužbe. Bolniki, ki jemljejo zaviralce TNF, so bolj občutljivi za resne okužbe. Uporabo zdravila Remicade prekinite, če se pri bolniku pojavi nova resna okužba ali sepsa, in mu uvedite ustrezno protimikrobno ali protiglivično terapijo, dokler ne bo okužba obvladana. Pred začetkom zdravljenja z zdravilom Remicade, morate vse bolnike pregledati in preiskati, da ugotovite morebitno aktivno ali neaktivno tuberkulozo. Če se pri bolnikih, zdravljenih z zdravilom Remicade, razvije resna sistemska bolezen, je treba posumiti na invazivno glivično okužbo, kot so aspergiloza, kandidiaza, pnevmocistoza, histoplazmoza, kokcidioidomikoza ali blastomikoza, poleg tega pa je pri teh bolnikih že zgodaj v poteku preiskav potreben posvet z zdravnikom, ki ima strokovno znanje iz diagnostike in zdravljenja invazivnih glivičnih okužb. Bolnike, pri katerih obstaja tveganje za okužbo z virusom hepatitisa B, je treba oceniti, ali imajo znake okužbe s HBV, preden smete pri njih uvesti zdravljenje z zdravilom Remicade. Bolnike s simptomi ali znaki motenj delovanja jeter morate pregledati oz. opraviti preiskave, da ugotovite morebitne znake poškodbe jeter. Kombiniranje zdravila Remicade in abatacepta oz. anakinre ni priporočljivo. Priporočamo, da živih cepiv ne dajete sočasno. Pri pediatričnih bolnikih s Crohnovo boleznijo če je le mogoče opravite vsa cepljenja, v skladu s tekočimi veljavnimi smernicami za cepljenje otrok, preden pri njih uvedete zdravljenje z zdravilom Remicade. Relativno pomanjkanje TNFα kot posledica anti TNF terapije lahko sproži avtoimunski proces. Infliksimab in druga zdravila, ki zavirajo TNFα, so bila v redkih primerih povezana z nevritisom vidnega živca, epileptičnimi napadi in novim pojavom ali poslabšanjem kliničnih simptomov in/ali z rentgenskimi znaki demielinizirajoče bolezni osrednjega živčevja, vključno z multiplo sklerozo in demielinizirajoče bolezni perifernega živčevja, vključno z Guillain Barréjevim sindromom. Pri odločanju o uvedbi zdravljenja pri bolnikih, ki so težki kadilci in imajo zato povečano tveganje za nastanek rakave bolezni, je potrebna previdnost. Glede na sedanje znanje ni mogoče izključiti tveganja za pojav limfomov ali drugih malignih bolezni pri bolnikih, zdravljenih z zaviralci TNF. Previdnost je potrebna tudi pri odločanju o uvedbi zdravljenja z zaviralci TNF pri bolnikih z rakavimi boleznimi v pretekli anamnezi ter pri odločanju o tem, ali naj nadaljujete z zdravljenjem pri bolnikih, pri katerih se pojavi nov nova rakava bolezen. Zdravilo Remicade morate uporabljati previdno pri bolnikih z blagim srčnim popuščanjem (razred I/II po NYHA). Pri bolnikih, ki so jemali zaviralce TNF, vključno z zdravilom Remicade, so poročali o pojavu pancitopenije, levkopenije, nevtropenije in trombocitopenije. Pri bolnikih, zdravljenih z zdravilom Remicade, ki so bili stari 65 let ali več, je bila incidenca resnih okužb večja kot pri bolnikih, ki so bili mlajših od 65 let. Pri zdravljenju starostnikov je torej treba posvetiti posebno pozornost tveganju za nastanek okužbe. Obstajajo znaki, da sočasna uporaba metotreksata in drugih imunomodulatorjev pri bolnikih z revmatoidnim artritisom, psoriatičnim artritisom in Crohnovo boleznijo zmanjša tvorbo protiteles proti infliksimabu in poveča koncentracijo infliksimaba v plazmi. Ni videti, da bi imeli kortikosteroidi klinično pomemben vpliv na farmakokinetiko infliksimaba. **NEŽELENI UČINKI:** Najpogostejši neželeni učinek zdravila, o katerem so poročali v kliničnih preskušanjih, je bila okužba zgornjih dihal, ki se je pojavila pri 25,3 % bolnikov, zdravljenih z infliksimabom, in pri 16,5 % bolnikov iz kontrolne skupine. Med najresnejše, z uporabo zaviralcev TNF povezane neželene učinke zdravila, o katerih so poročali pri uporabi zdravila Remicade, sodijo reaktivacija HBV, kronično srčno popuščanje, resne okužbe (vključno s sepso, oportunističnimi okužbami in TB), serumska bolezen (pozne preobčutljivostne reakcije), hematološke reakcije, sistemski eritematozni lupus/lupusu podoben sindrom, demielinizirajoče bolezni, dogodki v zvezi z jetri ali žolčnikom, limfom, hepatosplenični limfom celic T (HSTCL), črevesni ali perianalni absces (pri Crohnovi bolezni) ter resne z infuzijo povezane reakcije. **NAČIN IN REŽIM IZDAJE ZDRAVILA:** Zdravilo je zaradi svojih lastnosti, svoje relativne novosti ali zaradi varovanja javnega zdravja namenjeno izključno za zdravljenje, ki ga je mogoče spremljati samo v bolnišnici. **IMETNIK DOVOLJENJA ZA PROMET Z ZDRAVILOM:** Janssen Biologics B.V., Einsteinweg 101, 2333-CB-Leiden, Nizozemska. **DATUM ZADNJE REVIZIJE BESEDILA:** 02/2012. **TISKANO V SLOVENIJI:** junij 2012. Za dodatne informacije pokličite na predstavništvo Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana, tel: 01/5204 349, faks 01/5204 350.

LITERATURA: Povzetek glavnih značilnosti zdravila Remicade. **IZDAL IN ZALOŽIL:** Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana. **SAMO ZA STROKOVNO JAVNOST. DERM-1044434-0000 EXP: 06/2014**

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Acquired melanocytic nevi in Egyptian patients: A clinicopathological study

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Abstract

Introduction: Melanocytic nevi (MN) are the most important simulants of melanoma. Although acquired nevi are usually clinically stable, they may show abnormal clinical behavior. This study assessed the histological changes and prognosis of acquired MN with changing clinical behavior in Egyptian patients.
Methods: The study included 236 patients that were classified into two groups; Group A included nevi with abnormal clinical presentation and Group B included clinically typical nevi.
Results: Each group included 118 patients with a predominance of female patients. Abnormal clinical presentation in Group A included altered pigmentation (35.6%), rapid enlargement (30.5%), keratotic changes (16.9%), inflammation (7.6%), ulceration (5.1%), and hemorrhage (4.2%). Typical histological features were significantly higher ($p = 0.008$) in Group B (99.2%) compared with Group A (87.3%). Atypical histological features were significantly higher ($p = 0.002$) in Group A, with higher numbers of ulcerative and altered pigmented nevi. Malignant changes showed no significant difference ($p = 0.47$) between the two groups. No relapse was recorded after excision of any lesion.
Discussion: Among Egyptians, changing clinical behavior of MN may show histological atypia but low risk of malignant transformation. Early excision and follow-up of ulcerative and altered pigmented nevi are recommended.

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Introduction

Melanocytic nevi (MN) are considered the most important simulants of melanoma (MM) and it may be difficult to distinguish between the two lesions either clinically or histologically. Although most MN are stable and do not progress to malignancy, some nevi could be considered important risk markers and potential precursors of MM. Such nevi include dysplastic nevi (DN), congenital MN, and, to a lesser extent, acquired (common) MN (1).

Dysplastic (atypical) nevi remain an issue of controversy despite extensive investigation. On clinical grounds, the term “atypical MN” is more appropriate, whereas “dysplastic MN” describes histological characteristics. The association with MM is complex and it is often difficult to distinguish histologically between DN and MM. It is accepted that DN are characterized clinically by large size (> 5 mm in diameter) and show a mixture of marked discoloration, whereas histologically they are characterized by intradermal lentiginous hyperplasia, cytological atypia, and stromal response in addition to architectural atypia (2).

Although malignant transformation is uncommon in acquired MN, there are risk factors that increase the incidence of malignant transformation of MN. An increased number of MN has been suggested as a strong risk factor for MM (3), and sun exposure was considered the main environmental risk factor for the development of both MN and MM (4). Moreover, the similar causal pathway of some MN and MM has also led to considering these MN as precursor lesions of MM (5).

Melanocytic nevi in specific anatomical sites such as acral, genital, and flexural areas may also show unusual architecture and cytological atypia that can mimic DN and sometimes MM (6). This study recorded the clinical changes and analyzed the histological features and prognosis of acquired MN among Egyptian patients.

Material and methods

A retrospective randomized controlled study included cases diagnosed as acquired MN during the period from 2007 to 2011 at Al-Azhar University Hospitals, Cairo, Egypt. Clinical data were retrieved for each patient, including age, sex, skin type, and duration of the lesion in addition to the clinical characteristics of the lesion such as site, size, and morphology. Results of general skin examination and regional lymph nodes were also recorded to identify any associated skin tumors or abnormal changes of regional lymph nodes.

Data were collected from the computerized file system of the patient in addition to medical photography of the lesion. Because dermoscopy was only recently made available at the author’s department and only a few cases in this study were evaluated by dermoscopy, it was not considered as a main tool in evaluating the lesions. All of the lesions were surgically excised as a first-line management. Cases that had been previously treated with nonsurgical methods (such as laser) were excluded from the study.

Lesions were classified according to their clinical presentation into two groups: MN that showed abnormal clinical presentation were categorized as Group A, and MN with clinically typical presentation were categorized as Group B (used as a control group). Abnormal clinical presentations included any changes in size, shape, consistency, color, or surface of the nevus. Clinically typical nevi were symptom-free and they were only excised for cosmetic purposes.

Histologically, the lesions were classified as typical, atypical, or malignant. The histological criteria of typical MN were the presence of nests of melanocytes / nevus cells that are distributed at the dermoepidermal junction (junctional nevus), confined to the dermis (intradermal nevus), or with both components

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Atypical histological features included poor circumscription, asymmetry, irregular confluent nests, predominance of single melanocytes, cytological atypia, frequent mitosis, and presence of necrosis (7).

Any lesion showing one or more of these criteria was reviewed by three pathology experts for further evaluation and categorization of the lesion: either atypical or malignant. The diagnosis was confirmed by the opinion of two reviewers. Immunohistochemical staining using monoclonal antibodies for S100, HMB-45, and Ki-67 was carried out for specimens that showed atypical features.

The study was approved by the local ethics committee and patients' written consent was obtained for medical photography and skin biopsy. Data were collected and statistically analyzed using SPSS version 16. For quantitative data, the mean and standard deviation were calculated. The difference between two means was statistically analyzed using Student's t test. Chi-square x2 was used to analyze between numbers in two (or more) independent groups. A p value ≤ 0.05 was considered statistically significant.

Results

The study included 236 patients that were classified into two groups, each group formed of 118 patients. The majority of patients were females (64%) and the mean age at the time of diagnosis 39.6 ± 5.34 years. The duration of the lesions before excision ranged from 3 to 22 years with a majority of more than 10 years' duration (46.2%). Patients with skin type III were predominant (58.9%) and the majority of lesions (85.6%) were less than 1 cm in diameter. Skin examination showed the presence of other MN in 103 patients (43.6%) and other benign skin tumors in 31 patients (13.1%). The head and neck represented the most common anatomical site (55.5%), with a predominance of facial lesions in Group A and scalp lesions in Group B. A comparison between the two groups is summarized in Table 1.

Table 1 | **Demographic data of Egyptian patients with acquired melanocytic nevi.**

	Group A (N = 118) n (%)	Group B (N = 118) n (%)	Total (N = 236) n (%)
Sex			
Female	70 (59.3)	81 (68.6)	151 (64)
Male	48 (40.7)	37 (31.4)	85 (36)
Age			
Range	19–68	24–61	19–68
Mean ± SD	41.3 ± 6.52	37.9 ± 4.16	39.6 ± 5.34
Lesion duration			
‹ 5 years	13 (11)	35 (29.7)	48 (20.3)
5–10 years	38 (32.2)	41 (34.7)	79 (33.5)
› 10 years	67 (56.8)	42 (35.6)	109 (46.2)
Skin type			
Type III	66 (56)	73 (61.9)	139 (58.9)
Type IV	41 (34.7)	44 (37.3)	85 (36)
Type V	11 (9.3)	1(0.8)	12 (5.1)
Lesion site			
Head & neck	86 (72.9)	45 (38.1)	131 (55.5)
– Scalp	*24*	*32*	*56*
– Face	*48*	*5*	*53*
– Neck	*14*	*8*	*22*
Trunk	18 (15.2)	32 (27.1)	50 (21.2)
Upper limbs	8 (6.8)	19 (16.1)	27 (11.4)
Lower limbs	6 (5.1)	22 (18.6)	28 (11.9)
Lesion size			
‹ 1 cm	84 (71.2)	118 (100)	202 (85.6)
› 1 cm	34 (28.8)	0 (0)	34 (14.4)
Other melanocytic nevi	56 (47.5)	47 (39.8)	103 (43.6)
Other benign skin tumors	13 (11)	18 (15.3)	31 (13.1)

It was observed that most of scalp lesions were excised due to increased liability to trauma (especially during combing), whereas a few cases were excised due to clinical suspicion of adnexal tumor. On the other hand, most of the facial lesions were excised for cosmetic purposes, location near the eyes, and location on the beard or mustache areas interfering with shaving.

The abnormal clinical behavior of MN in Group A was in the form of altered pigmentation (35.6%), rapid increase in size (30.5%), verrucal or seborrheic keratosis-like changes (16.9%), inflammatory changes (7.6%), ulceration (5.1%), and angiomatous or vascular changes (with a pyogenic granuloma-like appearance or a variable degree of hemorrhage) (4.2%). Demographic data and histological spectrum in relation to atypical clinical forms of MN in Group A are shown in Table 2.

Histological analysis of rapidly enlarged nevi (Fig. 1) showed the presence of large fat lobules (fatty nevus) in 13 cases and pseudovascular or pseudolymphatic spaces in seven cases. Concomitant presence of sebaceous hyperplasia was observed in 10 cases, and in seven cases there was an epidermal or trichilemmal cyst. In five cases there was no significant histological finding.

Nevi with keratotic changes revealed two histological variants; a papillomatous type and a seborrheic keratosis–like type that also showed papillomatosis in addition to marked hyperkeratosis and numerous horn cysts. Both types were darkly pigmented with increased melanin pigmentation in the epidermis and upper dermal nests (Fig. 2). Atypical changes were observed in 10% of keratotic nevi and only 2.8% of enlarged nevi, and none of them showed malignant transformation.

Angiomatous nevi were characterized histologically by a mixture of nevocellular nests and various-sized vascular spaces in addition to variable degrees of intradermal hemorrhage (Fig. 3). Inflammatory nevi showed a ruptured hair follicle in seven cases (Fig. 4), and spongiotic dermatitis with crust formation (Meyerson's phenomenon) was observed in two cases. Neither inflammatory nor angiomatous nevi showed any atypical features or malignant transformation. In the majority of cases, dermal nests of nevus cells were easily recognized by routine histological examination. However, in some cases immunostaining with S100 was required to identify the nevus cells.

Histological analysis showed the predominance of intradermal nevi (67%) compared with compound nevi (27.1%) and junctional nevi (5.9%). Atypical histological features were significantly higher (p = 0.002) in Group A (11%) compared to Group B (0.8%). Out of 13 cases that showed atypical histological features in Group A, nevi with altered pigmentation (five cases) and nevi with surface ulceration (five cases) represented the majority of cases. The most striking histological findings included the presence of numerous atypical cells, dermal nevomelanocytes with large pleomorphic nuclei, and atypical features of dermal nests in addition to focal or sporadic staining for HMB-45 and Ki-67 (Fig. 5).

Malignant transformation was proved in only 1.7% of clinically abnormal MN without a significant difference between the two groups (Table 3). The first lesion of malignant transformation was proved in a compound nevus that was located on the thigh and showed increased pigmentation, enlarged size, and ulceration. The second lesion was a junctional nevus on the sole that showed altered pigmentation with increased size.

Follow-up was recorded for all nevi with atypical and malignant features for 1 year. Recurrence was recorded in three cases of atypical nevi and total excision was performed for all cases without relapse. Although nevi with malignant transformation showed no recurrence of the lesion, lymph node metastasis was recorded in both cases after 2 and 9 months, respectively.

Table 2 | **Clinical characteristics and histological spectrum of acquired melanocytic nevi in Group A.**

	Pigmented nevi (n = 42)	Enlarged nevi (n = 36)	Keratotic nevi (n = 20)	Inflamed nevi (n = 9)	Ulcerative nevi (n = 6)	Angiomatous nevi (n = 5)	Total N (%)
Sex							
Female	23	26	11	5	4	1	70 (59.3)
Male	19	10	9	4	2	4	48 (40.7)
Age							
Range	19–62	22–54	22–68	37–55	27–44	41–57	19–68
Mean ± SD	40.7 ± 5.26	39.2 ± 3.81	43.5 ± 8.45	49.4 ± 2.55	35.1 ± 4.87	47.6 ± 4.87	41.3 ± 6.52
Lesion duration							
‹ 5 years	7	3	0	3	0	0	13 (11)
5–10 years	18	9	4	5	1	1	38 (32.2)
› 10 years	17	24	16	1	5	4	67 (56.8)
Skin type							
Type III	20	27	6	7	3	3	66 (56%)
Type IV	17	6	12	2	2	2	41 (34.7%)
Type V	5	3	2	0	1	0	11 (9.3%)
Lesion site							
Head & neck	32	29	10	6	5	4	86 (72.9)
– Scalp	*5*	*14*	*2*	*2*	*1*	*0*	*24*
– Face	*20*	*14*	*2*	*4*	*4*	*4*	*48*
– Neck	*7*	*1*	*6*	*0*	*0*	*0*	*14*
Trunk	5	5	8	0	0	0	18 (15.2)
Upper limbs	3	1	1	2	0	1	8 (6.8)
Lower limbs	2	1	1	1	1	0	6 (5.1)
Lesion size							
‹ 1 cm	28	29	17	6	2	3	85 (72)
› 1 cm	14	7	3	3	4	2	33 (28)
Histological spectrum							
Typical	36	35	18	9	0	5	103 (87.3%)
Atypical	5	1	2	0	5	0	13 (11%)
Malignant	1	0	0	0	1	0	2 (1.7%)

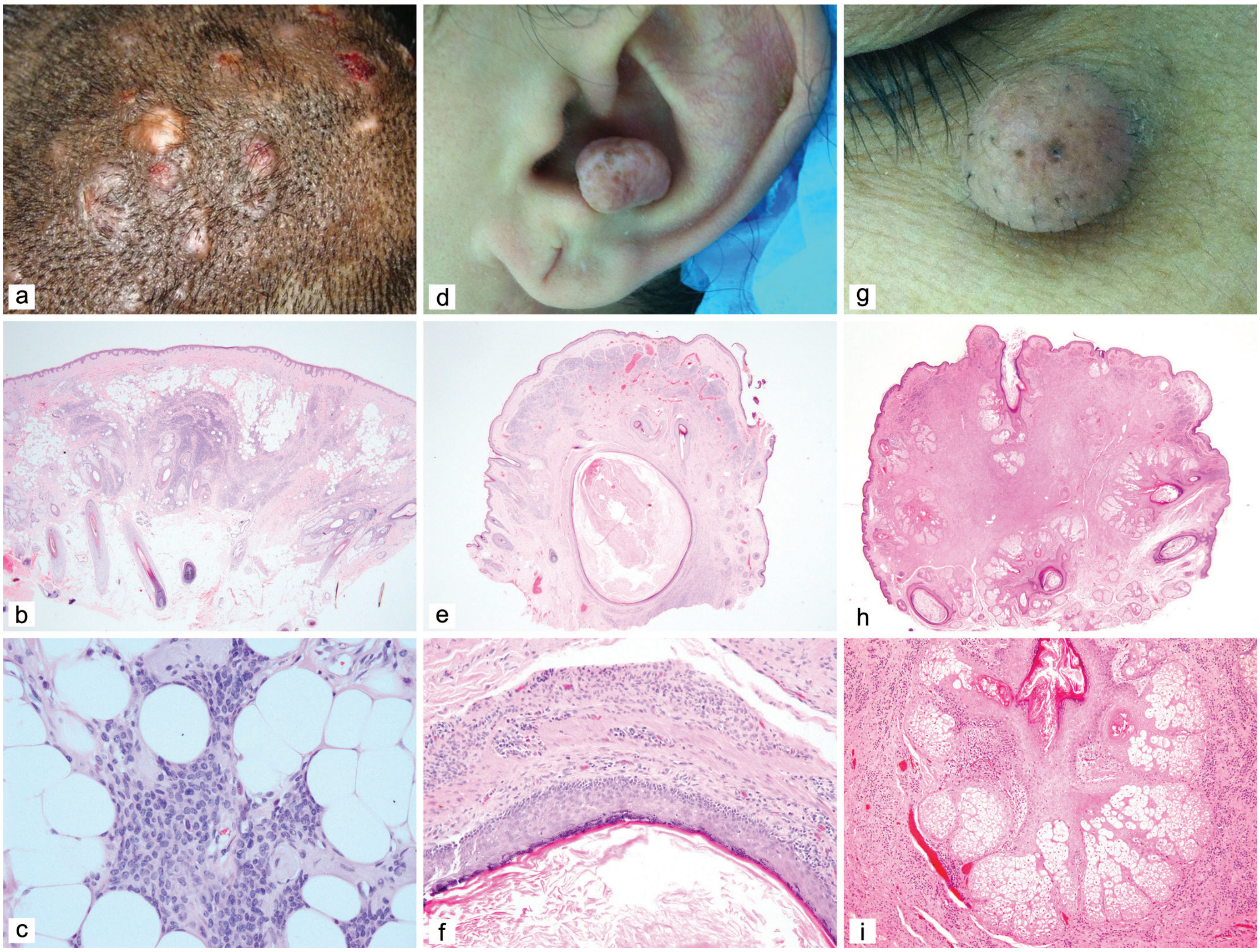

Figure 1 | Rapidly enlarged nevi on the scalp (a), ear (d), and face (g). Histological examination showed marked accumulation of fat cells (fatty nevus) (b and c, HE × 20 and × 400), large epidermal cysts (e and f, HE × 20 and × 400), and sebaceous hyperplasia (h and i, HE × 20 and × 400).

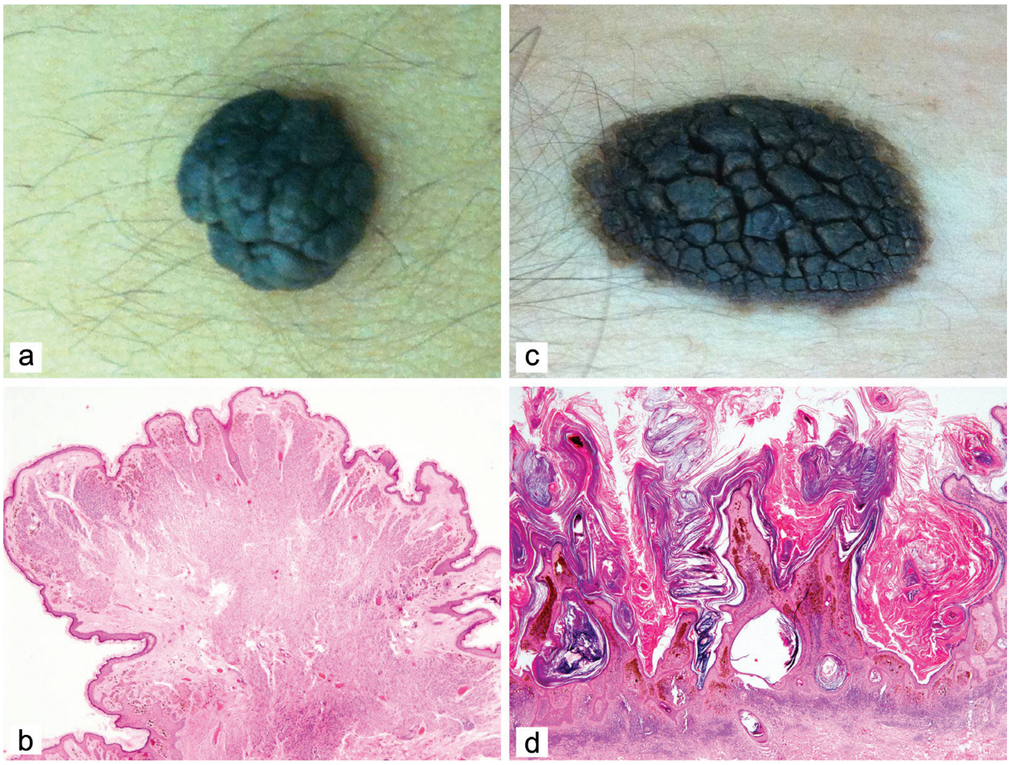

Figure 2 | Keratotic nevi presented with large pigmented lesions, either pedunculated nodule (a) or well-demarcated plaque (c). Histological examination showed either marked papillomatosis (b, HE × 40) or seborrheic keratosis–like changes with formation of many horn cysts (d, HE × 100).

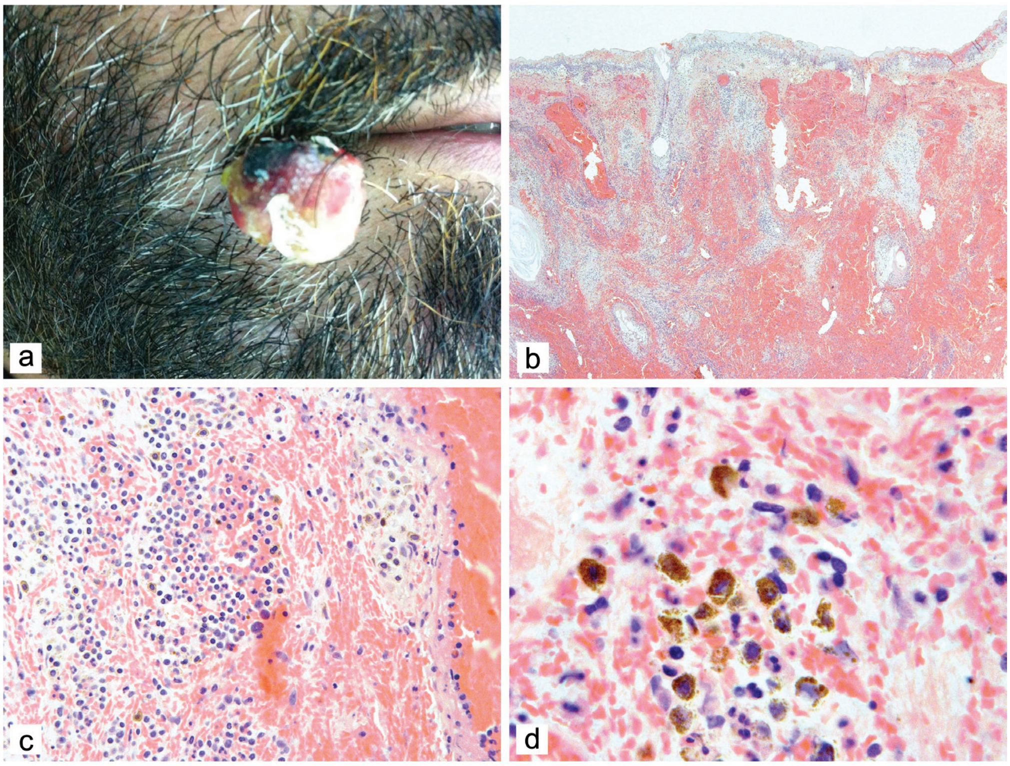

Figure 3 | Angiomatous nevus on the mouth angle (a) showed surface ulceration (b, HE × 20) with prominent hemorrhage (c, HE × 200) and mixed nevus cells with RBCs (d, HE × 1,000).

Table 3 | Association between histological features of acquired melanocytic nevi in both groups.

	Nevi with typical histological features		Nevi with atypical histological changes		Nevi with malignant transformation	
	Group A	Group B	Group A	Group B	Group A	Group B
Dermal type	78	92	1	0	0	0
Compound type	22	6	9	1	1	0
Junctional type	3	9	3	0	1	0
Total	103 (87.3%)	117 (99.2%)	13 (11%)	1 (0.8%)	2 (1.7%)	0 (0%)
p value	0.008		0.002		0.47	

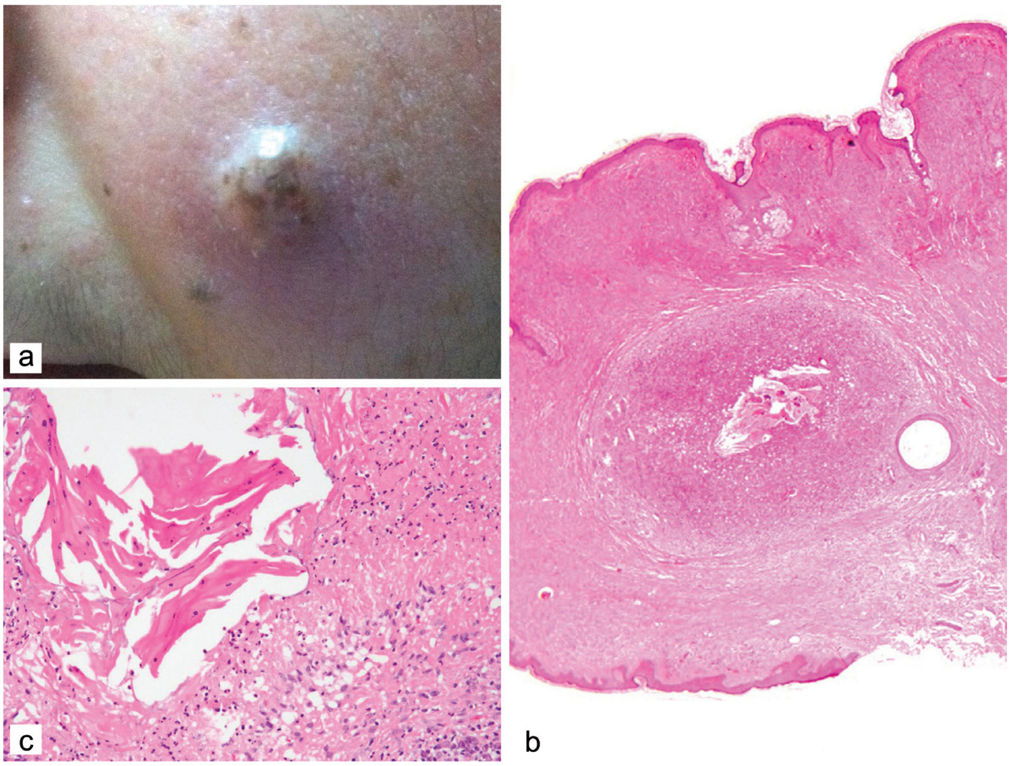

Figure 4 | Inflamed nevus on the cheek (a) showed ruptured hair follicle on the mid dermis (b, HE × 20) with mixed inflammatory reaction surrounding keratinous debris (c, HE × 400).

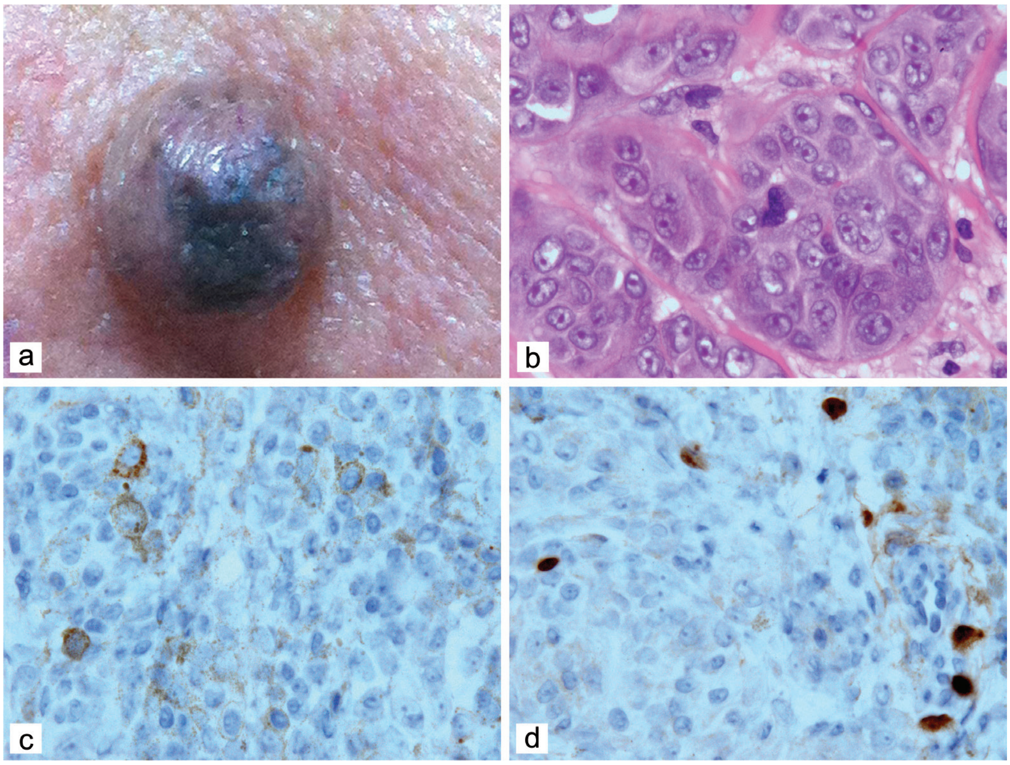

Figure 5 | Ulcerative nevus on the face (a) showed sporadic atypical cells within the dermal nests (b, HE × 1000). Some cells were positive for HMB-45 stain (c, immunostain × 400) whereas other cells were positive for Ki-67 stain (d, immunostain × 400).

Discussion

Melanocytic nevi among the Egyptian population are believed to have a benign course, and surgical excision is usually requested either for cosmetic purpose or due to changes in clinical behavior with the fear of melanoma transformation. It was found that there is increased incidence of benign MN in middle-aged individuals and in females of all ages, whereas DN and MM were more common in males, with a higher incidence of MM among the older age group (8).

It is widely accepted that there are several recognizable melanocytic precursors of cutaneous melanoma. The common melanocytic precursors include dysplastic MN, congenital nevi (of any size), acral MN, and darkly pigmented lesions of mucous membranes (9). It was suggested that early recognition of these melanocytic precursor lesions, particularly in high-risk individuals, and careful photographic follow-up or prophylactic excision of these lesions may be the most effective means of reducing the morbidity and mortality of cutaneous melanoma (10).

In the current study, malignant transformation was only proved in 1.7% of MN with atypical clinical presentation, whereas in clinically typical MN there was no malignant transformation in any case. Although the proper estimation of the transformation rate needs a wide-scale study with a large number of cases, this study's results suggest a low incidence of malignant transformation of MN among the Egyptian population. In agreement with this suggestion, Tsao et al. also concluded that the risk of malignant transformation of moles is low, especially in younger individuals. However, MN that persist into old age have an increased risk of malignant transformation (11). In this study, the effect of age on the prognosis of MN was almost eliminated by the presence of a matched-age control group.

Atypical MN not only increases the chance of progression to MM but also predisposes the patient to development of MM at other sites. Salava et al. found that clinically atypical and microscopically dysplastic nevi can be associated with an increased incidence of melanoma (12). Kang et al. also found that the risk of melanoma in individuals with atypical nevi is significantly greater than expected and the elevated risk was demonstrated even though careful, regular evaluations and removal of more atypical lesions were performed (13).

Although there was no record of any cutaneous melanoma diagnosed in patients with clinically atypical MN, this could be attributed to the low incidence of skin cancer among Egyptians (only representing 5% of the malignant tumors of the entire body). Moreover, there is low incidence of MM (8%) compared with other malignant epidermal tumors such as basal cell carcinoma (77%) and squamous cell carcinoma (15%) (14). These results were in agreement with Carli et al. (15), who found that the presence of large nevi and clinically atypical nevi among Italians did not result in an increased risk for cutaneous melanoma when the number of acquired MN was considered.

In this study, malignant transformation was observed in junctional and compound nevi, but not in any intradermal nevus. This may have contributed to the higher proliferative activity of nevus cells during the first stages, whereas with an intradermal nevus the cells become fully matured. It was suggested that MM arising from a nevus is more characterized by abrupt transition, localized distribution of junctional atypical cells, and the presence of dense dermal nests. Moreover, MM arising from acquired or congenital nevi are predominantly composed of roundish, monomorphous cells, whereas melanomas arising either de novo or from dysplastic nevi were characterized by markedly pleomorphic cells (16).

In this study, atypical histological features were significantly higher in MN with abnormal clinical behavior compared with clinically typical MN, and these changes were observed more among ulcerative and pigmented nevi. The most striking histological features in dysplastic lesions included cytological atypia, irregular confluent nests, and scattered mitosis. The correlation between clinical atypia and histological dysplasia was variable in previous reports. It was suggested that DN cannot be considered a distinct clinicopathological entity because histological dysplasia is found in a range of nevi that may or may not show clinical atypia (17).

Callaghan et al. found that the clinical characteristics associated with histological dysplasia include a macular component, irregular borders, and the presence of three or more colors, whereas asymmetry, diameter greater than 5 or 6 mm, and progression were not associated with atypical histological characteristics (18). However, Barnhill and Rouch found that nevus size, irregular border, ill-defined border, macular component, and pink color were associated significantly with histological dysplasia. Among these features, nevus size and irregular borders were more correlated with histological atypia (19). These reports suggested the difficulty in correlation between clinical atypia and histological dysplasia of MN.

There was also a controversy about the presence of atypical histological features in acquired MN. It was reported that atypical histological features among acquired MN might be present in 72% or 87.8% of cases (20, 21), This led to reinforcing the concept that DN could not be fully accepted as a distinctive histological entity because the histological features can also observed in nevi that are not classifiable as DN by other clinical and histological criteria (21). It was also suggested that lesions that have taken the critical step of violating the upper size limit of acquired MN might be the most favorable candidates for consideration of the diagnosis of DN (22).

One of the limitations of this study was the absence of dermoscopy features, which is an important tool in evaluating pigmented skin lesions. Although this would be appropriate in developed countries, in most developing countries and for most general dermatologists dermoscopy is usually not available and the main evaluation of pigmented lesions is based on clinical experience. This study could be beneficial in increasing the clinical awareness of variable changes of acquired MN among dermatologists, especially in developing countries.

Conclusion

Among Egyptian patients, acquired MN with abnormal clinical behavior are associated with significant histological atypia but a low risk of malignant transformation. Ulceration and altered pigmentation are important clinical clues for histological atypia. Early excision, careful histological examination, and close monitoring of such nevi are recommended.

References

1. Elder DE. Precursors to melanoma and their mimics: nevi of special sites. Mod Pathol. 2006;19:S4-20.
2. Rivers JK, Cockerell CJ, McBride A, Kopf AW. Quantification of histologic features of dysplastic nevi. Am J Dermatopathol. 1990;12:42-50.
3. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Abeni D, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur J Cancer. 2005;41:28-44.
4. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer. 2005;41:45-60.
5. Elder DE, Clark WH, Elenitsas R, Guerry D 4th, Halpern AC. The early and intermediate precursor lesions of tumor progression in the melanocytic system: common acquired nevi and atypical (dysplastic) nevi. Semin Diagn Pathol. 1993;10:18-35.
6. Hosler GA, Moresi JM, Barrett TL. Nevi with site-related atypia: a review of melanocytic nevi with atypical histologic features based on anatomic site. J Cutan Pathol. 2008;35:889-98.
7. Weedon D. Lentigines, nevi, and melanomas. In: Weedon D, editor. Weedon's skin pathology, 3rd ed. New York: Elsevier (Churchill Livingstone); 2010. p. 713-31.
8. Hussein MR, Elsers DA, Fadel SA, Omar AE. Clinicopathological features of melanocytic skin lesions in Egypt. Eur J Cancer Prev. 2006;15:64-8.
9. Skender-Kalnenas TM, English DR, Heenan PJ. Benign melanocytic lesions: risk markers or precursors of cutaneous melanoma? J Am Acad Dermatol. 1995;33:1000-7.
10. Rhodes AR. Melanocytic precursors of cutaneous melanoma. Estimated risks and guidelines for management. Med Clin North Am. 1986;70:3-37.

11. Tsao H, Bevona C, Goggins W, Quinn T. The transformation rate of moles (melanocytic nevi) into cutaneous melanoma: a population-based estimate. Arch Dermatol. 2003;139:282-8.
12. Salava A, Ranki A, Saksela O. [Dysplastic melanocytic nevus]. Duodecim. 2010; 126:2492–501. Finnish.
13. Kang S, Barnhill RL, Mihm MC, Fitzpatrick TB, Sober AJ. Melanoma risk in individuals with clinically atypical nevi. Arch Dermatol. 1994;130:999-1001.
14. Hussein MR. Skin cancer in Egypt: a word in your ear. Cancer Biol Ther. 2005;4: 593-5.
15. Carli P, Biggeri A, Giannotti B. Malignant melanoma in Italy: risks associated with common and clinically atypical melanocytic nevi. J Am Acad Dermatol. 1995;32:734-9.
16. Longo C, Rito C, Beretti F, Cesinaro AM, Piñeiro-Maceira J, Seidenari S, et al. De novo melanoma and melanoma arising from pre-existing nevus: in vivo morphologic differences as evaluated by confocal microscopy. J Am Acad Dermatol. 2011;65:604-14.
17. Annessi G, Cattaruzza MS, Abeni D, Baliva G, Laurenza M, Macchini V, et al. Correlation between clinical atypia and histologic dysplasia in acquired melanocytic nevi. J Am Acad Dermatol. 2001;45:77-85.
18. Morales-Callaghan AM, Castrodeza-Sanz J, Martínez-García G, Peral-Martínez I, Miranda-Romero A. Correlation between clinical, dermatoscopic, and histopathologic variables in atypical melanocytic nevi. Actas Dermosifiliogr. 2008; 99:380-9. Spanish.
19. Barnhill RL, Roush GC. Correlation of clinical and histopathologic features in clinically atypical melanocytic nevi. Cancer. 1991;67:3157-64.
20. Urso C. Atypical histologic features in melanocytic nevi. Am J Dermatopathol. 2000;22:391-6.
21. Klein LJ, Barr RJ. Histologic atypia in clinically benign nevi. A prospective study. J Am Acad Dermatol. 1990;22:275-82.
22. Cramer SF. Atypical histologic features in melanocytic nevi. Am J Dermatopathol. 2001;23:160-1.

Navodilo za predpisovanje

Ime zdravila – Daivobet 50 mikrogramov/500 mikrogramov v 1 g gel

Terapevtske indikacije – Topikalno zdravljenje psoriaze na lasišču pri odraslih. Topikalno zdravljenje blage do zmerne psoriaze v plakih na koži po telesu (psoriaza vulgaris) pri odraslih.

Odmerjanje in način uporabe – Daivobet gel nanašamo na prizadete dele enkrat dnevno. Priporočljivo trajanje zdravljenja je 4 tedne za lasišče in 8 tednov za kožo po telesu. Če je po tem obdobju potrebno nadaljevati ali ponovno uvesti zdravljenje, se lahko zdravljenje nadaljuje po zdravniškem pregledu in pod rednim zdravniškim nadzorom. Pri uporabi zdravil, ki vsebujejo kalcipotriol, maksimalni dnevni odmerek ne sme presegati 15 g. Zdravil, ki vsebujejo kalcipotriol, ne smemo uporabljati na površini, večji od 30 % telesne površine. Pred uporabo pretresite stekleničko in nanesite Daivobet gel na prizadeto mesto. Daivobet gela se ne sme nanesti neposredno na obraz ali oči. Po uporabi si umijte roke. Za doseganje optimalnega učinka, prhanje ali kopanje oziroma umivanje lasišča takoj po nanosu Daivobet gela ni priporočljivo. Daivobet gel naj učinkuje na koži čez noč ali čez dan. Pediatrična populacija: varnost in učinkovitost Daivobet gela pri otrocih, mlajših od 18 let, nista bili dokazani, zato uporabe Daivobet gela pri omenjeni populaciji ne priporočamo.

Kontraindikacije – Preobčutljivost za zdravilni učinkovini ali katerokoli pomožno snov. Daivobet gel je kontraindiciran pri eritrodermični, eksfoliativni in pustulozni psoriazi. Ker Daivobet gel vsebuje kalcipotriol, je kontraindiciran pri bolnikih z znanimi motnjami presnove kalcija. Ker Daivobet gel vsebuje kortikosteroid, je prav tako kontraindiciran pri naslednjih obolenjih: virusne (npr. herpes ali varicella) lezije kože ter glivične in bakterijske okužbe, okužbe s paraziti, spremembe na koži zaradi tuberkuloze ali sifilisa, perioralni dermatitis, atrofija kože, strije, krhke vene v koži, ihtioza, akne vulgaris, akne rozacea, rozacea, razjede, rane, perianalni ali genitalni pruritus.

Posebna opozorila in previdnostni ukrepi – Bolnika je treba podučiti o pravilni uporabi zdravila, da se izogne nanosu ali naključnemu prenosu zdravila na obraz, usta in oči. Po vsaki uporabi si je potrebno umiti roke, da preprečimo nehoteni prenos zdravila na omenjene predele. Daivobet mazilo vsebuje močan steroid skupine III, zato se je potrebno izogibati sočasni uporabi drugih kortikosteroidov. Neželeni učinki, ki so jih ugotovili pri sistemskem zdravljenju s kortikosteroidi, kot npr. supresija delovanja skorje nadledvične žleze ali pa vpliv na nadzor sladkorne bolezni, se lahko zaradi sistemske absorpcije zdravila pojavijo tudi med topikalnim zdravljenjem s kortikosteroidi. Izogibati se moramo tudi uporabi kortikosteroidov pod okluzivnimi povoji, saj se s tem poveča njihova sistemska absorpcija. Izogibati se moramo uporabi zdravila na velikih predelih prizadete kože, na sluznicah ali v kožnih gubah, saj se s tem sistemska absorpcija kortikosteroidov poveča. Ker zdravilo vsebuje kalcipotriol, se ob prekoračitvi največjega dnevnega odmerka (15 g) lahko pojavi hiperkalciemija. Ko zdravljenje prekinemo, se koncentracija kalcija v serumu hitro normalizira. Pri zdravljenju psoriaze s topikalnimi kortikosteroidi obstaja nevarnost nastanka generalizirane pustulozne psoriaze, ob prekinitvi zdravljenja z njimi pa lahko pride do povratnega učinka (rebound effect). Zato priporočamo zdravniško kontrolo tudi v času po končanem zdravljenju. Pri dolgotrajni uporabi se poveča tveganje za pojav lokalnih in sistemskih neželenih učinkov zaradi kortikosteroida. V primeru pojava neželenih učinkov zaradi dolgotrajne uporabe kortikosteroidov je potrebno zdravljenje prekiniti. Izkušenj s kombinacijo Daivobet mazila in drugih topikalnih izdelkov za zdravljenje psoriaze na istem predelu, sočasno sistemsko uporabo drugih zdravil za zdravljenje psoriaze oziroma sočasno uporabo fototerapije ni na voljo.

Medsebojno delovanje z drugimi zdravili ter druge oblike interakcij – Študij medsebojnega delovanja niso izvedli

Nosečnost in dojenje – Nosečnost: Daivobet gel se med nosečnostjo lahko uporablja le, če potencialne koristi opravičujejo morebitno tveganje. Dojenje: Pri predpisovanju Daivobet gela doječim materam, je potrebna previdnost. Bolnico je potrebno poučiti, da v času dojenja ne uporablja Daivobet gela na prsih.

Neželeni učinki – Pri približno 8 % bolnikov, ki so uporabljali Daivobet gel, so se pojavili neželeni učinki, ki pa niso bili resni. Učinki, med katerimi so večinoma različne reakcije na koži, najpogosteje pruritus, so običajno blagi. Občasno se pojavijo: poslabšanje psoriaze, pekoč občutek v koži, bolečine in draženje kože, folikulitis, dermatitis, eritem, akne, suha koža,izpuščaj, pustulozni izpuščaj. Naslednji neželeni učinki so najverjetneje povezani s farmakološkimi skupinami kalcipotriola oziroma betametazona: Kalcipotriol – Neželeni učinki vključujejo: reakcije na mestu aplikacije zdravila, pruritus, draženje kože, pekoč in bodeč občutek v koži, suho kožo, eritem, izpuščaj, dermatitis, ekcem, poslabšanje psoriaze, fotosenzitivnost in preobčutljivostne reakcije, vključno z zelo redkimi primeri angiodema in obraznega edema. V zelo redkih primerih se po topikalni uporabi lahko pojavijo sistemski učinki, kot npr. hiperkalciemija ali hiperkalciurija. Betametazon (v obliki dipropionata) – Lokalne reakcije, ki se lahko pojavijo po topikalni uporabi, še posebej, če ta traja dalj časa, vključujejo atrofijo kože, teleangiektazije, strije, folikulitis, hipertrihozo, perioralni dermatitis, alergijski kontaktni dermatitis, depigmentacijo in koloidno milio. Pri zdravljenju psoriaze obstaja možnost nastanka generalizirane pustulozne psoriaze. Sistemski učinki so pri topikalni uporabi kortikosteroidov pri odraslih redki, so pa lahko hudi. Lahko se pojavijo zaviranje delovanja skorje nadledvične žleze, katarakta, infekcije, vpliv na nadzor sladkorne bolezni in povišanje intraokularnega tlaka, zlasti po dolgotrajni uporabi. Sistemski učinki se pogosteje pojavijo, če zdravilo uporabimo pod okluzijo (plastika, kožne gube), pri uporabi zdravila na velikih površinah kože ali po dolgotrajni uporabi.

Preveliko odmerjanje – Uporaba odmerkov, večjih od priporočenih, lahko povzroči zvišanje koncentracije kalcija v serumu, ki pa se hitro zniža, ko zdravljenje prekinemo. Dolgotrajna topikalna uporaba prevelikih odmerkov kortikosteroidov lahko zavre delovanje hipofize in nadledvične žleze, kar povzroči sekundarno adrenalno insuficienco, ki je običajno reverzibilna. V takšnih primerih je indicirano simptomatsko zdravljenje. V primeru kronične toksičnosti je zdravljenje s kortikosteroidi potrebno postopno prekiniti.

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Factitious disorders in adults: two cases of unusual skin ulcers

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Abstract

The factitious disorders (FDs) include a large group of dermatological conditions characterized by skin lesions that patients themselves self-inflict but deny their active participation. FDs usually represent a diagnostic challenge, and their therapeutic management is usually based on a multidisciplinary approach because most FRD patients also suffer from undiagnosed behavior and personality disorders. We report two cases of FD: one patient that was suffering from severe depression and induced third-degree chemical burns on his own lower limbs, and another patient affected by obsessive-compulsive disorder and anorexia nervosa that presented with deep self-inflicted ulcers on her face. Our multispecialist approach, based on close cooperation between dermatologists and psychiatrists, led to a significant improvement of clinical conditions in both cases. Dermatologists need to be aware that FDs are complex disorders and a multidisciplinary approach is usually recommended to control their clinical course.

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Introduction

Factitious disorders (FDs), also known as dermatitis artefacta or pathomimia, describe a set of faked of self-inflicted skin lesions created without a clear external incentive. Patients deny any role in the creation of the lesions due to possible dissociative episodes. These self-inflicted skin injuries are most commonly derived from prolonged and deliberate scratching with the bare hands, but sometimes patients induce skin lesions by means of sharp tools or other instruments (1).

FDs are classified as primary psychiatric disorders according to the DSM-IV-TR classification (2). Depression and anxiety are the two most frequent psychiatric disorders among FD patients (3). Patients usually show a previous history of emotional disturbances both during childhood and in adult life, which leads them to have feelings of isolation and insecurity. This situation drives patients to develop dissociative personality disorders as a primary defense mechanism, which can promote self-harm behavior as a way of dealing with traumatic events (3, 4).

FDs mainly affect women in late adolescence or early adult life. Their clinical manifestations are highly variable and do not conform to common dermatoses. The morphology of self-inflicted lesions depends on the tools used by patients and ranges from common manifestations such as erosions, ulcerations, fissures, and burns to less common features such as purpura, bruising, cheilitis, alopecia, edema, and nail dystrophy. Lesions are often located in skin areas that the patient can easily reach (e.g., the face, arms, legs, neck, and back) (4).

In this case series we briefly describe the diagnostic and therapeutic approach to two cases of FD that came to our attention.

Report of two cases

Case 1

A 76-year-old man was referred to our clinical observation for the presence of two ulcerative skin lesions, located on the legs in mirror-image locations. The lesions were painful and they had appeared 2 months earlier. Physical examination revealed two deep ulcerative lesions of 5 × 10 and 6 × 8 cm, respectively, with erythematous, sharp edges that reached to the underlying muscles (Fig. 1).

These lesions resulted from a self-harm practice initiated by the patient himself: family members reported that he self-injected diesel fuel, which caused deep, third-degree chemical burns. The patient was therefore admitted to our clinic for medical and surgical management. Cutaneous examination failed to reveal any dermatological diseases, and routine blood tests were within the normal range.

The psychiatric examination confirmed a diagnosis of anxiety and depression triggered by some critical episodes in his life: a partial gastrectomy due to gastric cancer and the recent death of his wife. Afterwards, long-term systemic treatment with psychotropic drugs was introduced by psychiatrists (citalopram 20 mg/day and alprazolam 2 mg/day). The ulcerative lesions were initially treated with curettage and topical medications such as hydrocolloid and hydrogel, and then with skin grafts (Fig. 2a, b).

Figure 1 | Deep ulcer on the leg caused by self-injection of diesel fuel.

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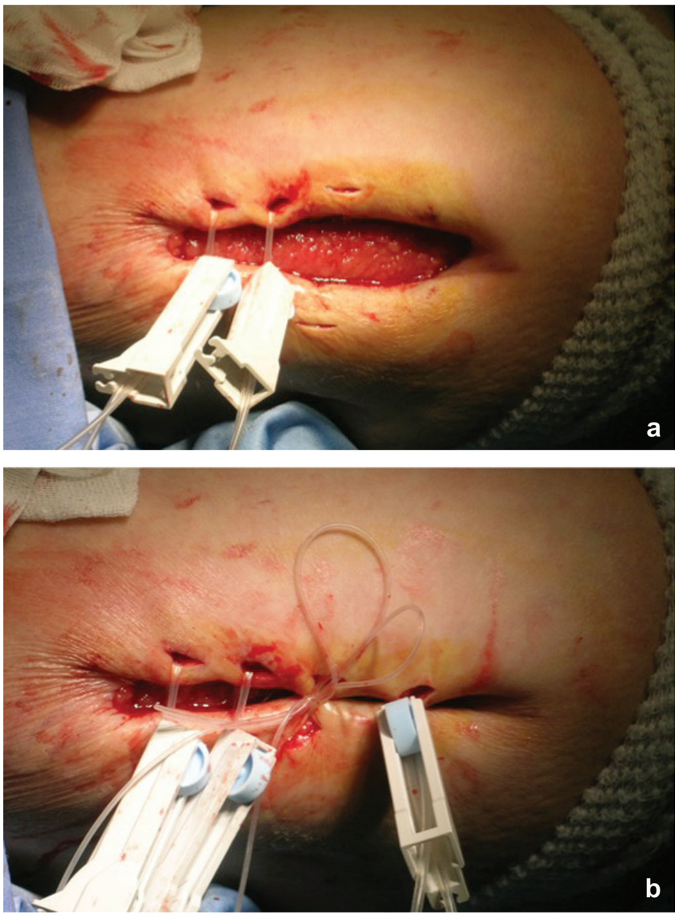

Figure 2a,b | Surgical treatment of the ulcer: application of skin grafts.

Case 2

A 40-year-old woman came to our attention for a single, round, ulcerative lesion 2 cm in diameter with mildly erythematous edges, located in the mandibular region (Fig. 3). The patient reported that she had been suffering from ulcerative lesions on the face for about 6 years, in a chronic and relapsing mode. She claimed to have already consulted many other dermatologists to solve this problem without any clinical improvement despite the treatments received.

Figure 3 | Circular ulcerative lesion on the mandibular region self-inflicted by the patient.

However, the patient was unable to describe the prior treatments or produce previous prescriptions. During hospitalization she reported, despite considerable reluctance, congenital retinitis pigmentosa, congenital bilateral deafness, and a 12-year history of anorexia nervosa from the age of 26. Therefore she was sent for a psychiatric consultation that revealed a psychiatric profile characterized by previous anorexia nervosa with its typical features, such as body weight below the index of normality, secondary amenorrhea, obsessive-phobic beliefs about her body, self-induced vomiting, and dangerous feelings during the ideation of food. She also reported persistent, casual purgative practices and obsessive-compulsive personality traits, with a tendency toward perfectionism and self-blame, hypersensitivity to criticism, social withdrawal, and difficulty in managing self-directed aggression, expressed by explosive events.

The patient revealed that when stressful moments occurred, compulsive behavior generally emerged, aimed at reducing her anxiety: episodes of compulsive eating and vomiting and self-harm rituals were present. A skin biopsy was not performed due to the patient's reluctance. Thus an ex-adiuvantibus therapy with psychotropic drugs and psychotherapy support was started (sertraline 100 mg/day and delorazepam 15 droplets three times a day).

The dermatological approach relied on advanced occlusive dressings in order to minimize the possibility that the patient would manipulate the skin lesion. In about 6 months a slow healing of the wound started to be evident, accompanied by the patient's increasing awareness regarding its origin.

Discussion

According to Koo's classification (5), psychodermatological disorders can be grouped as:

1. Psychophysiological disorders, in which the patient's emotional processes determine the severity of dermatosis;
2. Psychiatric disorders that precede self-induced skin injuries;
3. Secondary psychiatric disorders that are secondary to a dermatological disease;
4. Cutaneous sensory disorders, in which the patient complains about itching or burning sensations without visible skin manifestations.

FDs are included in primary psychiatric disorders and several studies show that they are related to serious psychiatric illnesses such as schizophrenia, personality disorders, and dementia (3). Although the overall incidence of FD is not known, the importance of psychological involvement is emphasized by its strong association with borderline personality disorder and its higher prevalence in patients diagnosed with anorexia and bulimia (33%) (6). Diagnosis is often difficult because FD can be confused with other dermatoses and patients are reluctant to admit the real origin of their lesions. They typically show a "Mona Lisa–like" expression of artful innocence and they refuse psychiatric support but, at the same time, they tend to be demanding and manipulative (7).

The fear of missing organic diseases may induce a physician to request major and unnecessary analyses and therapies, which can also shift the focus away from the underlying emotional distress. In fact, the treatment cannot be separated from a psychiatric approach, which must support the dermatological treatments from the start of the patient's course of care.

The dermatological management of FD is difficult and variable, and it depends on the anatomical site and the patient's way of producing cutaneous manifestations (8, 9). Affected areas are usually easy to reach with various objects such as blades, knives, and other sharp objects. Patients can also induce injuries simply with their hands or by self-injecting caustic or toxic substances into the skin. Sometimes it is also necessary to treat complications such as infections and scars (10–13).

Advanced medical devices can be used, and the gold standard is the occlusive dressing because it protects the patient from self-manipulation. In the first case report, the clinical diagnosis was easy to obtain thanks to information provided by patient's family. However, for the second patient the clinical diagnosis was obtained only after a careful multidisciplinary study of the case. We agree that it is unhelpful, and sometimes even damaging, to acknowledge patients' psychological disorders, as reported by many others in the literature (14). An admission of personal involvement is not necessary at all because it shakes patients' psychic defenses and may lead them to change doctors. In our cases, the early approach to the diseases was based on "how" and not on "why." In this way it was possible to first obtain the patients' confidence and cooperation and then their acceptance of the psychiatric care that is essential for a complete recovery.

References

1. Rodríguez Pichardo A, García Bravo B. Dermatitis artefacta: a review. Actas Dermosifiliogr. 2013. pii: S1578-2190(13)00237-0. doi: 10.1016/j.adengl.2012.10.018.
2. Doran AR, Roy A, Wolkowitz OM. Self-destructive dermatoses. Psychiatr Clin North Am. 1985;8:291-8.
3. Mohandas P, Bewley A, Taylor R. Dermatitis artefacta and artefactual skin disease: the need for a psychodermatology multidisciplinary team to treat a difficult condition. Br J Dermatol. 2013;169:600-6.
4. Potenza C, Bernardini N, Mambrin A, Skroza N. Dermatitis artefacta in a patient affected by impulse control disorder: case report. Acta Dermatovenerol Croat. 2011;19:28-30
5. Koo JYM, Do JH, Lee CS. Psychodermatology. J Am Acad Dermatol. 2000;43:848-53.
6. Gattu S, Rashid RM, Khachemoune A. Self-induced skin lesions: a review of dermatitis artefacta. Cutis. 2009;84:247-51.
7. Gregurek-Novak T, Novac-Bilic G, Vucić M. Dermatits artefacta: unusual appearance in an older woman. J Eur Acad Dermatol Venereol. 2005;19:223-5.
8. Campanati A, Marconi B, Penna L, Paolinelli M, Offidani A. Pronounced and early acne in Apert's syndrome: a case successfully treated with oral isotretinoin. Eur J Dermatol. 2002;12:496-8.
9. Koblenzer CS. Dermatitis artefacta. Clinical features and approaches to treatment. Am J Clin Dermatol. 2000;1:47-55.
10. Campanati A, Savelli A, Sandroni L, Marconi B, Giuliano A, Giuliodori K, et al. Effect of allium cepa-allantoin-pentaglycan gel on skin hypertrophic scars: clinical and video-capillaroscopic results of an open-label, controlled, nonrandomized clinical trial. Dermatol Surg. 2010;36:1439-44.
11. Balakrishnan C, Erella VS, Vashi C, Jackson O, Vandemark S. Self-inflicted specific pattern burns in psychiatric patients. Can J Plast Surg. 2007;15:153-4.
12. Campanati A, De Blasio S, Giuliano A, Ganzetti G, Giuliodori K, Pecora T, et al. Topical ozonated oil versus hyaluronic gel for the treatment of partial- to full-thickness second-degree burns: A prospective, comparative, single-blind, non-randomised, controlled clinical trial. Burns. 2013;39:1178-83.
13. Campanati A, De Blasio S, Giuliano A, Ganzetti G, Giuliodori K, Pecora T, Consales V, et al. Response to Letter to the Editor: 'A precise knowledge of ozonated oils will help to define the favourable and peculiar properties of these functional dermatological matrices'. Burns. 2014. doi: 10.1016/j.burns.2013.12.013. In press.
14. Ahmed A, Bewley A, Taylor R. Dermatitis artefacta in vulnerable adult with a dissociative state. Clin Exp Dermatol. 2013;38:921-3.

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In situ malignant melanoma on nevus spilus in an elderly patient

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Abstract

Nevus spilus is the term usually given to a pigmented skin lesion, congenital or acquired, that may occur anywhere on the body, consisting of a large light tan patch with numerous superimposed darker scattered maculae or papulae that are flat or slightly raised. For a long time, nevus spilus was believed to be a benign lesion. However, in 1957 Perkinson reported a melanoma appearing on nevus spilus for the first time. Since then other reports about melanomas developing on nevus spilus have been published, sometimes with a fatal outcome. We describe the case of an 80-year-old male patient with a congenital nevus just above his left knee. The lesion had remained unchanged over time, but some months before his checkup the patient noticed a darker area in the lesion that had continued to enlarge. The lesion was removed and histological examination revealed an in situ malignant melanoma. Although nevus spilus is not normally considered a precursor of melanoma, the potentiality of malignant transformation requires regular monitoring, and careful checkups are recommended and justified.

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Introduction

The term *nevus spilus* (NS) refers to hyper-pigmented patches of various sizes and sites, congenital or acquired, characterized by multiple darker brown speckled maculae, flat or raised, inside.

NS is a relatively common condition whose prevalence varies from 0.2 to 2.3%. As a congenital nevus, NS can be classified into three distinct clinical types (1, 2); small if it is less than 1.5 cm, medium if it varies from 1.5 to 19.9 cm, and large if its diameter exceeds 20 cm. There also exists segmental NS, better known as zoniform or zosteriform NS. NS can be found anywhere on the body, but the most common location is on the chest and upper limbs, and often the arrangement of NS follows the lines of Blaschko (3). Two distinct types of NS have been described, in the form of macular versus papular NS, each one sometimes related to a specific syndrome (4). The speckles are often maculae rather than papulae and develop during a period of months to years, with the number of elements ranging from eight to 10, and in some cases up to 30 elements, generally in relation to the size of NS. They usually range from 1 to 3 mm, but there can be a wide variety of size. The background of NS shows the histological features of a lentigo simplex or a café au lait macule, whereas the speckles show the histological features of a variety of nevi: junctional, compound, intradermal, dysplastic, Spitz, blue, neurotized nevus, or ink spot lentigo (3). Although as a rule NS is not considered a precursor of melanoma, it must be monitored because it may turn into a malignant melanoma.

We describe an in situ malignant melanoma in an 80-year-old male that developed on a congenital NS.

Case report

In an 80-year-old male patient, a newly formed irregular colored patch appeared on the right thigh inside a pre-existing speckled NS and was referred as fast-growing. The NS had been present at birth and had not undergone any significant changes up to then. The patient's past medical history revealed the removal of a basal cell carcinoma and a malignant melanoma on his right leg 10 years earlier.

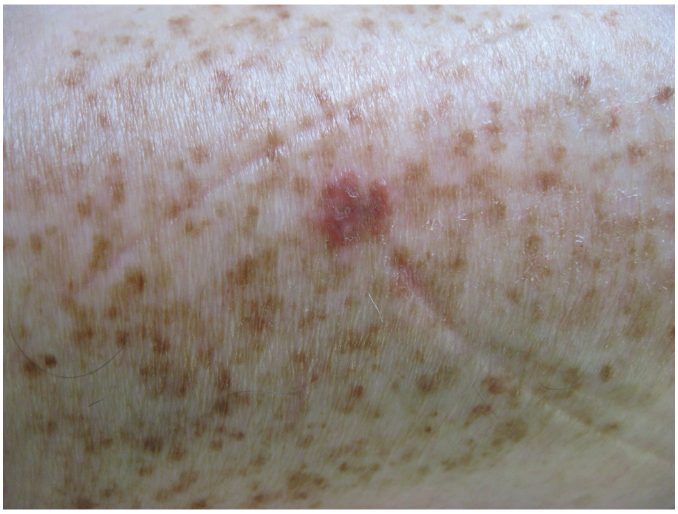

Figure 1 | Nevus spilus and melanoma. The examination shows the newly formed, tan to reddish-brown area arising on the congenital nevus spilus. The area is irregular and larger than the other speckles.

The clinical examination highlighted the presence of an oval-shaped patch, roughly 7 cm in diameter, pigmented, irregularly speckled with multiple random spread of flat maculae, darker than the patch itself (Fig. 2). More or less in the centre of the area there was a flat irregular 7 mm lesion, darker than the other maculae (Fig. 1).

The newly formed lesion was surgically removed and histopathologically showed to be "an in situ malignant melanoma" (Fig. 3a,b,c). Thereafter the patient was referred to a plastic surgeon for the complete removal of the remaining NS.

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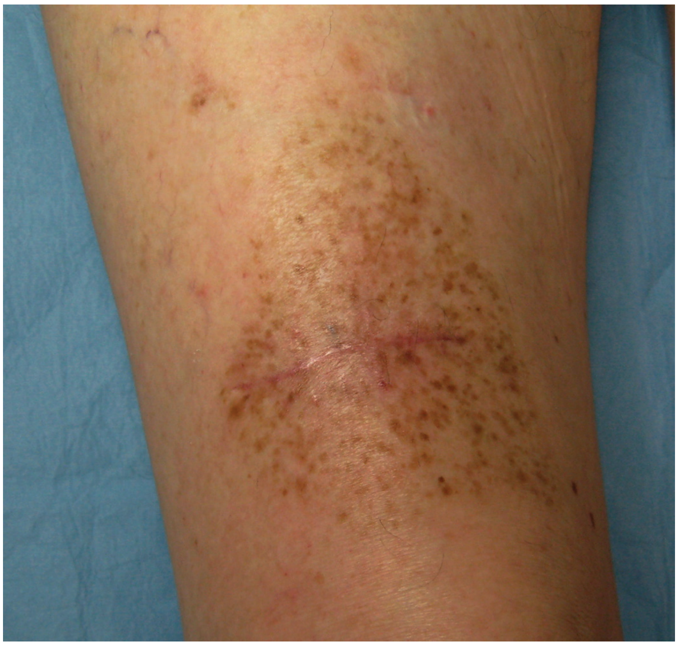

Figure 2 | The complete feature of nevus spilus after biopsy of the in situ malignant melanoma. The oval patch is irregularly speckled with multiple random spread of flat maculae darker than the patch itself.

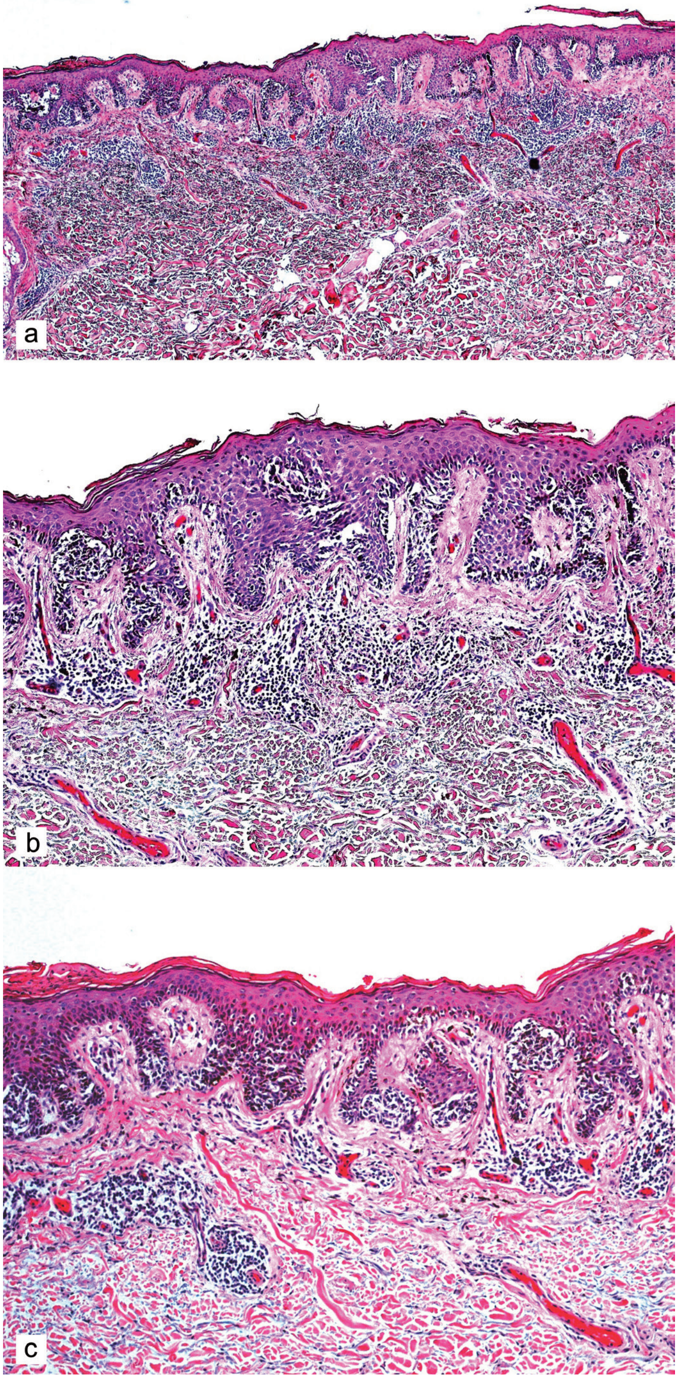

Figure 3a, b, c | Hematoxylin-eosin stain. Histopathological examination shows the characteristics of an in situ malignant melanoma, with the marked proliferation of atypical melanocytes along the dermal-epidermal junction, melanophage streams, and superficial inflammatory infiltration of the dermis. The raised melanocytes are inside the epidermis and do not create regular "nests".

Discussion

For a long time NS was believed to be a benign lesion and, even if the development of melanoma on NS is a rare event, its possible malignant change has been widely reported. In 1957 Perkinson (5) described for the first time a melanoma appearing on NS in a patient with neurofibromatosis. Since then, 35 or more cases of melanoma developing on NS have been published, sometimes with a fatal outcome (6–11).

Reviewing all of the literature published, melanoma on NS usually seems to arise in Caucasian or black patients, more frequently on the trunk than the limbs, with a female-male ratio of 56:44 (2); the average age of patients is 49, range 17–79 years. Melanoma on NS is usually only one neoplasm, but sometimes there can be more (11).

The melanoma most often found is superficial spreading melanoma (68%), followed by nodular melanoma (16%), and only in a few cases in situ melanoma. Abecassis et al. (10) reported that in 52% of melanoma cases the NS was already present at birth, in 33% it was acquired during infancy, and in 14% it appeared later. In 60% of cases, melanoma was generated in small- to medium-sized NS with an average of 7.4 cm, in 24% of cases in zosteriform NS, and in the remaining 16% in giant NS. Given the scant number of giant NS, this confirms the higher progressive risk of larger NS (8). The presence of a dysplastic nevus on a NS is quite frequent (32% of cases), but its relevance is unclear.

From the studies published, the malignant potential appears to vary from 0.13% to 0.2% and seems to be higher in NS than congenital melanocytic nevi (12). Worthy of note is the fact that the macular NS can evolve into a melanoma more frequently than papular NS (4, 13).

Based on these general data, it is not possible to predict which patients may develop a melanoma on a NS; however, some important conclusions can be drawn. The risk factor of malignant transformation seems to increase when the lesion is congenital or acquired in infancy, when its size is ≥ 4 cm, and when the type of NS is macular rather than papular, taking into account the importance of the "nestling" cells in the hyperpigmented patch.

In the case of a positive histological test, complete excision of the entire lesion is necessary, size permitting, in order to eliminate the "faulty background" and to search for any multifocal melanomas. However, it is not justified to systematically remove all lesions, bearing in mind the low incidence of NS degeneration, unless the monitoring of the NS is problematic either because of its body site or the patient's compliance. Finally, NS requires careful and closely individualized monitoring by dermatologists, and patients and relatives should be restricted to performing self- examination to detect early changes that may be the starting phase of turning malignant. Regular monitoring must also continue in elderly patients; a biopsy is recommended if a change is noticed in order to evaluate the histological features and decide about excision.

Despite the wide range of publications, the link between NS and melanoma still needs to be clarified. It is hoped that in the future targeted guidelines will be available for proper management of NS.

References

1. Sigg C, Pelloni F, Schnyder UW. Frequency of congenital nevi, nevi spili and café-au-lait spots and their relation to nevus count and skin complexion in 939 children. Dermatologica. 1990;180:118-23.
2. Corradin MT, Zattra E, Fiorentino R, Alaibac M, Belloni-Fortina A. Nevus spilus and case report and review of the literature. J Cutan Med Surg. 2010;14:85–9.
3. Hanayama H, Terashi H, Hashikawa K, Tahara S. Congenital melanocytic nevi and nevus spilus have a tendency to follow the lines of Blaschko: an examination of 200 cases. J Dermatol. 2007;34:159-63.
4. Vidaurri-de la Cruz H, Happle R. Two distinct types of speckled lentiginous nevi characterized by macular versus papular speckles. Dermatology. 2006;212:53-8.
5. Perkinson NG. Melanoma arising in café au lait spot of neurofibromatosis. Am J Surg. 1957;53:1018-20.
6. Kurban RS, Preffer FI, Sober AJ, Mihm MC Jr, Barnhill RL. Occurrence of melanoma in “dysplastic” nevus spilus: report of case and analysis by flow cytometry. J Cutan Pathol. 1992;19:423-8.
7. Karam SL, Jackson SM. Malignant melanoma arising within nevus spilus. Skinmed. 2012;10:100-2.
8. Cecchi R, Fancelli L, Troiano M. Melanoma arising in giant zosteriform nevus spilus. Indian J Dermatol Venereol Leprol. 2012;78:643-5.
9. Bolognia JL. Fatal melanoma arising in a zosteriform speckled lentiginous naevus. Arch Dermatol. 1991:127:240-1.
10. Abecassis S, Spatz A, Cazeneuve C, Martin-Villepou A, Clerici T, Lacour JP, et al. Melanome sur naevus spilus: 5 observations. Ann Dermatol Venereol. 2006;133:323-8. French.
11. Piana S, Gelli MC, Grenzi L, Ricci C, Gardini S, Piana S. Multifocal melanoma arising on nevus spilus. Int J Dermatol. 2006;45:1380-1.
12. From L. Congenital naevi—let’s be practical. Pediatr Dermatol. 1992;9:345–6.
13. Stella A, Ponholzer K, Weingast J, Binder M. Melanoma arising in a giant nevus spilus maculosus. Dermatol Pract Concept. 2011;1:21-4.

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Sestava in oblika zdravila: (1) Ena viala vsebuje 25 mg etanercepta. (2) Ena napolnjena injekcijska brizga vsebuje 50 mg etanercepta. (3) Ena viala vsebuje 10 mg etanercepta. Etanercept je pridobljen z rekombinantno DNA tehnologijo v ovarijskih celicah kitajskega hrčka. **Indikacije:** (1,2) Revmatoidni artritis (RA) - zmeren do hud aktiven RA pri odraslih (v kombinaciji z metotreksatom), kadar odziv na zdravljenje s protirevmatičnimi zdravili, ki vplivajo na imunsko odzivnost, vključno z metotreksatom (če ta ni kontraindiciran), ni zadosten. Monoterapija, kadar bolnik ne prenese metotreksata ali kadar trajno zdravljenje z njim ni primerno. Hud, aktiven in napredujoč RA pri odraslih, ki še niso dobivali metotreksata. (1,2,3) Juvenilni idiopatski artritis (JIA) - poliartritis (pozitiven ali negativen za revmatoidni faktor) in razširjen oligoartritis pri otrocih in mladostnikih, starih 2 leti ali več, ki so se nezadostno odzvali na zdravljenje z metotreksatom ali ga niso prenašali. Psoriatični artritis pri mladostnikih, starih 12 let ali več, ki so se nezadostno odzvali na zdravljenje z metotreksatom ali ga niso prenašali. Artritis, povezan z entezitisom, pri mladostnikih, starih 12 let ali več, ki so se nezadostno odzvali na konvencionalno zdravljenje ali ga niso prenašali. (1,2) Psoriatični artritis (PA) - aktiven in progresiven PA pri odraslih, če je bil odziv na zdravljenje s protirevmatičnimi zdravili, ki vplivajo na imunsko odzivnost, nezadosten. (1,2) Ankilozirajoči spondilitis (AS) - hud aktiven AS pri odraslih, če je bil odziv na konvencionalno zdravljenje nezadosten. (1,2) Psoriaza v plakih (PP) - zmerna do huda PP pri odraslih, ki se ne odzovejo na drugo sistemsko zdravljenje, vključno s ciklosporinom, metotreksatom ali psoralenom in ultravijolično svetlobo UV-A (PUVA), oziroma je pri njih drugo zdravljenje kontraindicirano ali ga ne prenašajo. (1,2,3) Otroška psoriaza v plakih - težka kronična psoriaza v plakih pri otrocih in mladostnikih od 6. leta starosti naprej, pri katerih se z drugo sistemsko terapijo ali fototerapijo bolezni ne da zadostno obvladati ali je bolniki ne prenašajo. **Odmerjanje in način uporabe:** Zdravljenje z Enbrelom lahko uvede in nadzoruje le zdravnik specialist, ki ima izkušnje z zdravljenjem navedenih stanj. Bolniki, ki se zdravijo z Enbrelom, naj prejmejo opozorilno kartico za bolnika. Odrasli (vse indikacije): 25 mg dvakrat na teden ali 50 mg enkrat na teden. *Psoriaza v plakih:* do 12 tednov je mogoče uporabljati tudi 50 mg dvakrat na teden, čemur sledi 25 mg dvakrat na teden ali 50 mg enkrat na teden, če je treba. Zdravljenje mora trajati do remisije, vendar največ 24 tednov. Za nekatere bolnike bo morda primerno stalno zdravljenje, daljše od 24 tednov. Če po 12 tednih ni odziva, je treba zdravljenje prekiniti. Če je indicirano ponovno zdravljenje, je odmerek 25 mg dvakrat na teden ali 50 mg enkrat na teden. Pediatrična populacija: *JIA:* Priporočeni odmerek je 0,4 mg/kg telesne mase (do največ 25 mg na odmerek) 2-krat na teden subkutano z razmikom med odmerki 3-4 dni ali 0,8 mg/kg (do največ 50 mg na odmerek) enkrat na teden. *Otroška psoriaza v plakih:* 0,8 mg/kg (do največ 50 mg na odmerek) enkrat na teden do največ 24 tednov. Če je indicirano ponovno zdravljenje, je odmerek 0,8 mg/kg (do največ 50 mg na odmerek) enkrat na teden. *Ukinitev zdravljenja:* o ukinitvi je treba razmisliti, če ni odziva po 4 mesecih (JIA) ali 12 tednih (otroška psoriaza v plakih) zdravljenja. Način uporabe: subkutana injekcija. **Kontraindikacije:** Preobčutljivost na zdravilno učinkovino ali katerokoli pomožno snov, sepsa ali možnost nastanka sepse ter aktivne okužbe, vključno s kroničnimi ali lokaliziranimi okužbami. **Posebna opozorila in previdnostni ukrepi:** Okužbe: Pred zdravljenjem, med njim in po njem je treba bolnike pregledati glede okužb in pri tem upoštevati, da je povprečni razpolovni čas odstranjevanja etanercepta iz telesa približno 70 ur (razpon 7-300 ur). Poročali so o primerih resnih okužb. Bolnike, pri katerih se med zdravljenjem pojavi nova okužba, je treba strogo nadzorovati. Zdravljenje je treba prekiniti, če pride do hude okužbe. Previdnost je potrebna pri zdravljenju bolnikov s ponavljajočimi se ali kroničnimi okužbami v anamnezi ali z drugimi osnovnimi stanji, ki bi lahko povečala dovzetnost za okužbe. Tuberkuloza: Pred začetkom zdravljenja je treba vse bolnike pregledati glede aktivne kot tudi neaktivne ('latentne') tuberkuloze. Priporočljivo je, da se ti testi vpišejo v bolnikovo opozorilno kartico. Obstaja nevarnost lažno negativnih rezultatov tuberkulinskega kožnega testa, posebno pri bolnikih, ki so težko bolni ali imunokompromitirani. Pri aktivni tuberkulozi zdravljenja ni dovoljeno uvesti, pri neaktivni ('latentni') tuberkulozi pa se mora pred uvedbo zdravljenja in v skladu z nacionalnimi priporočili začeti zdravljenje latentne tuberkuloze s tuberkulostatiki. Vsem bolnikom je treba naročiti, naj poiščejo zdravniško pomoč, če se med zdravljenjem ali po njem pojavijo znaki/simptomi tuberkuloze. Reaktivacija hepatitisa B: Pri bolnikih, ki so kdaj že bili okuženi s HBV in so se zdravili z antagonisti TNF, vključno z Enbrelom, so poročali o reaktivaciji hepatitisa B. Pred uvedbo zdravljenja je treba bolnike preiskati na okužbo s HBV. Če je bolnik pozitiven na HBV, je pred uvedbo zdravljenja priporočljivo posvetovanje s specialistom za zdravljenje hepatitisa B. Pri dajanju Enbrela bolnikom, okuženim s HBV, je potrebna previdnost. Take bolnike je treba ves čas zdravljenja in še več tednov po njem spremljati glede znakov in simptomov aktivne okužbe s HBV. Če se razvije okužba s HBV, je treba zdravljenje prekiniti in uvesti učinkovito protivirusno ter ustrezno podporno zdravljenje. Hepatitis C: Poročali so o poslabšanju hepatitisa C, potrebna je previdnost. Alergijske reakcije: poročali so o alergijskih reakcijah, vključno z angioedemom in urtikarijo, opisani pa so tudi primeri resnih reakcij. Če se pojavi kakršnakoli resna alergijska ali anafilaktična reakcija, je treba zdravljenje prekiniti in uvesti ustrezno zdravljenje. (2) Pokrovček igle vsebuje lateks, ki lahko povzroči preobčutljivostne reakcije, če z Enbrelom ravna oseba z znano ali možno preobčutljivostjo na lateks ali če ga damo takšni osebi. Imunosupresija: Za antagoniste TNF, vključno z Enbrelom, velja, da lahko vplivajo na naravno odpornost bolnika proti okužbam in malignim obolenjem. Bolniki, zelo izpostavljeni virusu noric, naj začasno prekinejo zdravljenje. Maligne in limfoproliferativne bolezni: Možnega tveganja za razvoj limfomov, levkemije ali drugih hematopoetičnih ali čvrstih rakavih obolenj ni možno izključiti. Previdnost je potrebna pri preudarku o uporabi antagonistov TNF pri bolnikih z anamnezo malignosti ali pri preudarku o nadaljevanju zdravljenja pri bolnikih, pri katerih se pojavi malignost. *Kožni rak:* Pri bolnikih, zdravljenih z antagonisti TNF, vključno z Enbrelom, so poročali o melanomu in nemelanomskem kožnem raku. Priporočamo občasen pregled kože. Cepljenja: Med zdravljenjem bolnik ne sme prejeti živih cepiv. Tvorba avtoprotiteles: Zdravljenje lahko sproži nastajanje avtoimunskih protiteles. Hematološke reakcije: Poročali so o redkih primerih pancitopenije in zelo redkih primerih aplastične anemije, tudi s smrtnim izidom. Posebna previdnost je potrebna pri bolnikih, ki imajo krvno diskrazijo v anamnezi. Vse bolnike in starše/skrbnike je treba opozoriti, da morajo v primeru pojava znakov ali simptomov, ki kažejo na krvno diskrazijo ali okužbo, med zdravljenjem takoj poiskati zdravniško pomoč. V primeru krvne diskrazije je treba zdravljenje prekiniti. Nevrološke bolezni: Pri bolnikih z demielinizirajočimi obolenji, ali pri tistih, ki imajo povečano tveganje zanje, je treba pred zdravljenjem skrbno pretehtati tveganja in koristi, vključno z nevrološko oceno. Kongestivno srčno popuščanje: Pri predpisovanju bolnikom s kongestivnim srčnim popuščanjem je potrebna previdnost. Izsledki sicer še niso dokončni, vendar podatki kažejo na morebitno tendenco k poslabšanju popuščanja pri bolnikih, zdravljenih z Enbrelom. Alkoholni hepatitis: Ne sme se uporabljati za zdravljenje alkoholnega hepatitisa. Previdnost je potrebna pri uporabi pri bolnikih, ki imajo tudi zmeren do težak alkoholni hepatitis. Wegenerjeva granulomatoza: Enbrela ni priporočljivo uporabljati za zdravljenje te bolezni. Hipoglikemija pri bolnikih, ki se zdravijo zaradi sladkorne bolezni: Med zdravljenjem so poročali o hipoglikemiji, zato bo morda treba zmanjšati odmerek zdravila proti sladkorni bolezni. Starejše osebe (≥65 let): Potrebna je previdnost, posebno pozornost je treba posvetiti pojavljanju okužb. Pediatrična populacija: Priporočamo, da pred začetkom zdravljenja, če je le mogoče, opravite vsa cepljenja v skladu z veljavnimi smernicami. Pri bolnikih z JIA, ki so se zdravili z Enbrelom, so poročali o kronični vnetni črevesni bolezni in uveitisu. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Sočasno zdravljenje z anakinro ali z abataceptom: klinična korist teh dveh kombinacij ni dokazana, zato nista priporočljivi. Sočasno zdravljenje s sulfasalazinom: potrebna je previdnost. **Plodnost, nosečnost in dojenje:** Ženske v rodni dobi morajo med zdravljenjem in še tri tedne po prenehanju tega uporabljati ustrezno metodo kontracepcije. Uporaba med nosečnostjo ni priporočljiva. Etanercept prehaja placento. Uporaba živih cepiv v prvih 16 tednih po tem, ko so matere dojenčkov prejele zadnji odmerek Enbrela, običajno pri dojenčkih ni priporočljiva. Bolnica mora med zdravljenjem prenehati dojiti ali pa prekiniti zdravljenje, pri čemer je treba upoštevati tako korist dojenja za otroka kot korist zdravljenja za mater. **Neželeni učinki:** Odrasli: *Zelo pogosti (≥ 1/10):* Okužbe (vključno z okužbami zgornjih dihal, bronhitisom, cistitisom in kožnimi okužbami), reakcije na mestu injiciranja (vključno s krvavitvijo, podplutbami, eritemom, srbenjem, bolečino in oteklino). *Pogosti (≥ 1/100 do < 1/10):* alergijske reakcije, nastanek avtoprotiteles, pruritus, zvišana telesna temperatura. Pediatrična populacija: Na splošno so bili neželeni učinki po vrsti in pogostnosti podobni tistim pri odraslih. Vrste okužb, opaženih v kliničnih preskušanjih pri bolnikih z JIA, starih 2-18 let, so bile na splošno blage do zmerne in skladne s tistimi, ki jih pogosto vidimo pri skupinah ambulantnih pediatričnih bolnikov. Resni neželeni učinki so bili: norice z znaki in simptomi aseptičnega meningitisa, ki se je pozdravil brez posledic, vnetje slepiča, gastroenteritis, depresija/osebnostne motnje, kožne razjede in ezofagitis/gastritis, streptokokni septični šok (streptokoki skupine A), diabetes mellitus tipa I in okužbe mehkih tkiv ter postoperativnih ran. V kliničnih preskušanjih pri bolnikih z JIA so poročali o 4 primerih sindroma aktivacije makrofagov. V obdobju trženja so pri bolnikih z JIA poročali o kronični vnetni črevesni bolezni in uveitisu. **Način in režim izdaje:** Rp/Spec. **Imetnik dovoljenja za promet:** Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, Velika Britanija. **Datum zadnje revizije besedila:** 9. 1. 2014 **Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.**

Literatura: 1. Povzetek glavnih značilnosti zdravila Enbrel, 9.1.2014 **2.** Yamauchi P. et al. The treatment of psoarisis and psoriatic arthritis with etanercept: pratical considerations on monotherapy, combination therapy, and safety. Dermatol Clin 22 (2004) 449-459. **3.** Data on file, Amgen, Inc. 2013. **4.** Povzetek glavnih značilnosti zdravila Remicade. 2013. Janssen Biologics B.V. **5.** Povzetek glavnih značilnosti zdravila Humira. 2013. Abbott Biotechnology Ltd. **6.** Povzetek glavnih značilnosti zdravila Orencia. 2013. Bristol-Myers Squibb Pharmaceuticals Ltd. **7.** Povzetek glavnih značilnosti zdravila Mabthera. 2013. Roche Products Ltd. **8.** Povzetek glavnih značilnosti zdravila Cimzia. July 2012. UCB Pharma SA. **9.** Povzetek glavnih značilnosti zdravila Simponi. September 2012. Janssen Biologics B.V.

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A case of inverse psoriasis successfully treated with adalimumab

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Abstract

Inverse psoriasis is a rare form of psoriasis characterized by the involvement of skin fold areas rather than the more common psoriatic involvement of the extensor surfaces of the extremities, trunk, and scalp. In addition, it requires a modified therapeutic approach because it is often less responsive to standard treatment regimens. Current treatment recommendations for inverse psoriasis mainly consist of topical agents, including corticosteroids, calcipotriol, and immunomodulating agents, whereas systemic medications remain insufficiently studied. Although adalimumab, a TNF-α inhibitor, has been approved for the treatment of moderate to severe plaque psoriasis, some reports indicate that TNF-α inhibitors may sometimes trigger psoriatic lesions, including inverse psoriasis. However, we present a case of inverse psoriasis and psoriatic arthritis unresponsive to standard treatment that was successfully treated with adalimumab.

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Introduction

Inverse (intertriginous) psoriasis is characterized by the involvement of skin fold areas such as the inguinal folds, gluteal cleft, axillae, and external genitalia, rather than the more common psoriatic involvement of the extensor surfaces of the extremities, trunk, and scalp (1). Some reports have indicated that tumor necrosis factor-α (TNF-α) inhibitors may induce psoriatic lesions, including inverse psoriasis (2). In contrast, we present a case of successful treatment of inverse psoriasis in a patient with psoriatic arthritis (PsA) with the TNF-α inhibitor adalimumab.

Case report

A 37-year-old Caucasian male with psoriasis and a history of dactylitis came to our rheumatology practice for assessment of hand oligoarthritis. He had had painful and swollen joints for the last 2 years and psoriatic lesions affecting the scalp that had been recurring for more than 10 years and were treated using topical corticosteroids. His psoriasis worsened 3 years ago when the lesions extended to the intergluteal area and the genitalia. While fungal infection was excluded, a skin biopsy revealed histological alterations consistent with psoriasis. Thus, topical pimecrolimus was initiated in addition to the topical corticosteroids previously prescribed. Despite transient improvement, co-therapy with pimecrolimus and corticosteroids failed to achieve long-term clinical relief after 18 months of regular use. At the time of examination at the rheumatology practice, the laboratory tests were unremarkable and the rheumatoid factor and anti-citrullinated protein antibodies were negative. The diagnosis of PsA was established according to the Classification of Psoriatic Arthritis (CASPAR) study group criteria. Non-steroidal anti-inflammatory drugs were prescribed. Six months later, the PsA had progressed to the small joints of both feet. He was therefore started on a disease modifying therapy with methotrexate (MTX) 15 mg qwk. After three weeks of MTX therapy, the patient complained of adverse events, including severe nausea with vomiting, headache, and insomnia. His arthritis was still active (Disease Activity Index (DAS28-ESR) 3.80) and his quality of life was adversely affected due to arthritis (Health Assessment Questionnaire: Patient-Reported Outcomes Measurement Information (HAQ-PROMIS) 1.25) and inverse psoriasis (Dermatology Life Quality Index (DLQI) 15). Considering the unbearable adverse effects, MTX was discontinued.

Because adalimumab, a fully humanized monoclonal antibody against TNF-α, is currently registered for treatment of PsA as well as moderate to severe plaque psoriasis (3), therapy with adalimumab was begun according to the national guidelines for the treatment of PsA. At the beginning of the treatment, erythematous macules, papules, and plaques were observed on the glans and the outer aspect of the foreskin, and erythema with erosions in the gluteal fold (Fig. 1, Day 0). After 90 days of treatment with adalimumab 40 mg once every 14 days by subcutaneous injection, not only was the arthritis in remission (DAS28-ESR 1.39), but an almost complete regression of the psoriatic lesions was also observed. Only small residual erythematous macules and papules remained on the glans and mild erythema in the gluteal cleft (Fig 2, Day 90). The patient's quality of life improved significantly (HAQ–PROMIS 0 and DLQI 1). After two visits to our rheumatology department during a 6-month follow-up, he is doing well, reports no adverse events of the adalimumab therapy, and has no psoriatic skin lesions.

Discussion

To our knowledge, this is the first report of successful treatment of inverse psoriasis with adalimumab. Indeed, our patient that received adalimumab for treatment of PsA concomitantly experienced almost a complete regression of intertriginous psoriasis, which had been resistant to conventional topical anti-psoriatic agents.

Inverse psoriasis presents in only 3 to 7% of psoriatic patients and differs from the more common psoriasis vulgaris in the localization of skin lesions as well as in the therapeutic approach. Namely, inverse psoriasis is less responsive to conventional therapy and often presents a therapeutic challenge (1). Due to the lack of internationally accepted guidelines for the treatment of inverse

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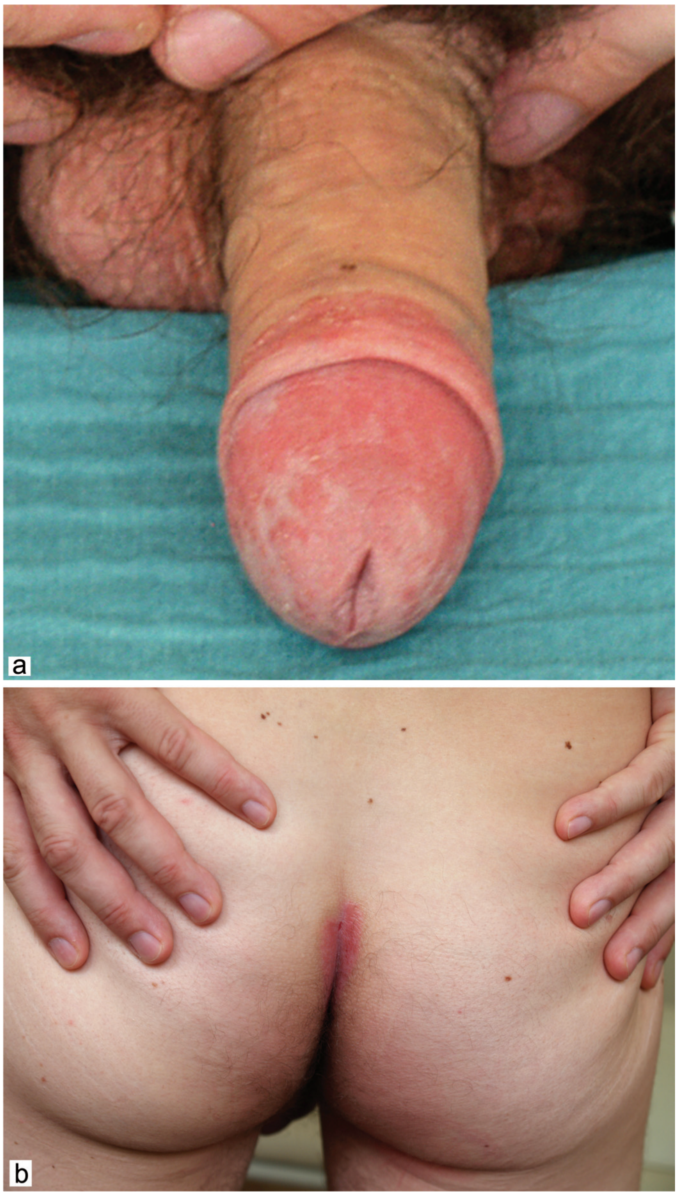

Figure 1 | Psoriasis of the penis and gluteal fold before treatment with adalimumab. (a) Penile psoriasis at the beginning of treatment; erythematous macules, papules, and plaques on the glans and outer aspect of the foreskin (Day 0). (b) Erythema with erosions in the gluteal fold at the beginning of treatment (Day 0).

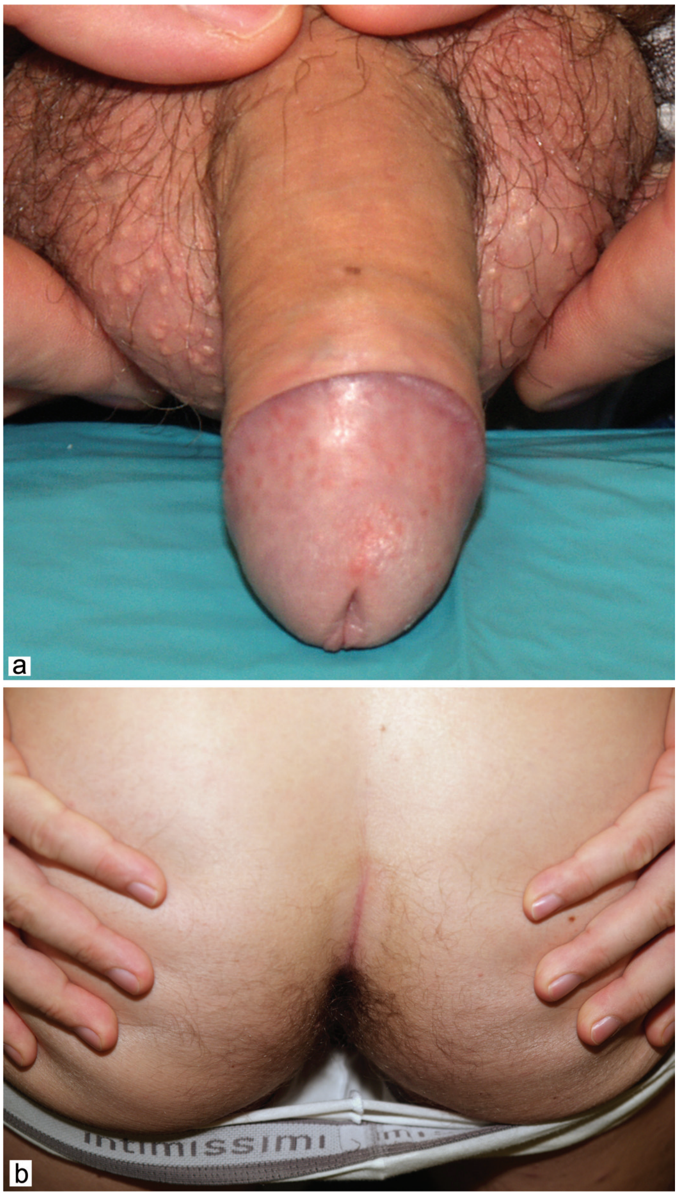

Figure 2 | Psoriasis of the penis and gluteal fold after treatment with adalimumab. (a) Small residual erythematous macules and papules on the glans after treatment (Day 90). (b) Almost complete regression of erythema in the gluteal fold after treatment (Day 90).

psoriasis, and also a lack of our own national guidelines, current treatment recommendations are based on the recently published consensus that includes mainly topical agents, such as corticosteroids for acute exacerbations and calcipotriene (calcipotriol) or immunomodulating agents (pimecrolimus or tacrolimus) for long-term therapy. A combination of these approaches is sometimes needed (4). The potential role of microorganisms in producing an inflammatory reaction in inverse psoriasis should also be considered and some patients may need appropriate antimicrobial therapy (4). The benefits of systemic treatment options have not been sufficiently studied. Nevertheless, as advocated by some experts, the use of systemic medications, including biologics, may have a role in the management of inverse psoriasis when topical medications are ineffective (4). Efalizumab, a biologic formerly available to treat psoriasis, has been used in some patients with severe inverse psoriasis with good results (1, 5).

Adalimumab, a TNF-α inhibitor, has been approved for the treatment of PsA and also, more recently, for moderate to severe plaque psoriasis (3). The use of these medications has expanded the pharmacological options for the treatment of psoriasis and revolutionized the therapeutic landscape. On the other hand, TNF-α inhibitors might sometimes worsen preexisting psoriasis or even trigger a new-onset of psoriasis through unknown mechanisms (6). Our case indicates that adalimumab may represent a viable treatment option for patients with inverse psoriasis unresponsive to standard treatments.

Conclusion

We describe the first case of the successful treatment of inverse psoriasis with adalimumab. Furthermore, our observations suggest that adalimumab may be considered as a treatment approach in inverse psoriasis that is resistant to conventional therapy. However, further clinical studies are needed to support this observation.

References

1. Syed ZU, Khachemoune A. Inverse psoriasis: case presentation and review. Am J Clin Dermatol. 2011;12:143-6.
2. Guerra I, Algaba A, Pérez-Calle JL, Chaparro M, Marín-Jiménez I, García-Castellanos R, et al. Induction of psoriasis with anti-TNF agents in patients with inflammatory bowel disease: a report of 21 cases. J Crohns Colitis. 2012;6:518-23.
3. Moore AY, Richardson BS. Long-term use of adalimumab in the treatment of moderate to severe plaque psoriasis: a review of the literature. Clin Cosm Invest Dermatol. 2010;3:49-58.
4. Kalb RE, Bagel J, Korman NJ, Lebwohl MG, Young M, Horn EJ, et al. Treatment of intertriginous psoriasis: from the medical board of the National Psoriasis Foundation. J Am Acad Dermatol. 2009;60:120-4.
5. George D, Rosen T. Treatment of inverse psoriasis with efalizumab. J Drugs Dermatol. 2009;8:74-6.
6. Schmidt E, Wetter DA, Ferguson SB, Pittelkow MR. Psoriasis and palmoplantar pustulosis associated with tumor necrosis factor-α inhibitor: the Mayo Clinic experience, 1998 to 2010. J Am Acad Dermatol. 2012;67:179-85.

Kako se lahko odraža učinkovito izboljšanje klinične slike

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HUMIRA
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ZDRAVI Z ZAUPANJEM

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Humira 40 mg raztopina za injiciranje v napolnjeni injekcijski brizgi.
Sestava: Bistra raztopina za injiciranje v napolnjeni injekcijski brizgi. Ena 0,8 ml napolnjena injekcijska brizga z enim odmerkom vsebuje 40 mg adalimumaba. Adalimumab je rekombinantno humano monoklonsko protitelo.
Terapevtske indikacije: Revmatoidni artritis: v kombinaciji z metotreksatom: zdravljenje zmernega do hudega aktivnega revmatoidnega artritisa pri odraslih bolnikih, kadar odziv na imunomodulirajoča zdravila, vključno z metotreksatom, ni zadosten; zdravljenje hudega, aktivnega in progresivnega revmatoidnega artritisa pri odraslih, ki prej še niso dobivali metotreksata. Poliartikularni juvenilni idiopatski artritis: v kombinaciji z metotreksatom za zdravljenje aktivnega poliartikularnega juvenilnega idiopatskega artritisa pri mladostnikih, starih od 13 do 17 let, ki se ne odzovejo ustrezno na eno ali več imunomodulirajočih antirevmatičnih zdravil. Psoriatični artritis: zdravljenje aktivnega in napredujočega psoriatičnega artritisa pri odraslih, če odziv na predhodno zdravljenje z imunomodulirajočimi antirevmatiki ni bil ustrezen. Ankilozirajoči spondilitis: zdravljenje hudega aktivnega ankilozirajočega spondilitisa pri odraslih, ki se na konvencionalno terapijo ne odzovejo ustrezno. Crohnova bolezen: zdravljenje hude, aktivne Crohnove bolezni pri bolnikih, ki se ne odzovejo na popoln in ustrezen ciklus zdravljenja s kortikosteroidom in/ali imunosupresivom, ali pa takšnega zdravljenja ne prenesejo oz. imajo zanj medicinske kontraindikacije.Psoriaza: zdravljenje zmerne do hude kronične psoriaze v plakih pri odraslih bolnikih, ki se ne odzovejo na druge sistemske terapije ali imajo kontraindikacije zanje.
Odmerjanje in način uporabe: Zdravljenje mora uvesti in nadzorovati zdravnik specialist. Revmatoidni artritis: odrasli bolnik: 40 mg adalimumaba vsak drugi teden v enkratnem odmerku v subkutani injekciji. Psoriatični artritis in ankilozirajoči spondilitis: 40 mg adalimumaba, apliciran v enkratni subkutani injekciji vsak drugi teden. Crohnova bolezen: med indukcijo pri odraslih bolnikih s hudo Crohnovo boleznijo 80 mg 0. teden in nato 40 mg 2. teden. Psoriaza: odrasli bolniki: začetni odmerek 80 mg subkutano, ki mu sledi 40 mg subkutano čez en teden in nato 40 mg subkutano vsak drugi teden. Otroci in mladostniki (stari od 13 do 17 let): bolniki s poliartikularnim juvenilnim idiopatskim artritisom, stari nad 13 let: 40 mg adalimumaba vsak drugi teden v enkratnem odmerku v subkutani injekciji.
Kontraindikacije: Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Aktivna tuberkuloza ali druge hude okužbe in oportunistične okužbe. Zmerno do hudo srčno popuščanje.
Posebna opozorila in previdnostni ukrepi: Okužbe: Bolniki so bolj dovzetni za resne okužbe. Okvarjena pljučna funkcija lahko zveča tveganje za razvoj okužbe. Bolnike je zato treba pred, med in po zdravljenju natančno kontrolirati glede okužb, vključno s tuberkulozo. Ker lahko eliminacija adalimumaba traja do pet mesecev, je treba bolnike ves ta čas nadzirati. Reaktivacija hepatitisa B: Pri bolnikih, ki so bili kronični nosilci virusa hepatitisa B, so opažali reaktivacijo hepatitisa B. Nevrološki zapleti: Antagonisti TNF, s Humiro vred, so bili v redkih primerih povezani s pojavom ali poslabšanjem kliničnih simptomov in/ali rentgenoloških znakov demielinizirajoče bolezni, vključno z multiplo sklerozo. Malignomi in limfoproliferativne bolezni: V kontroliranih delih kliničnih preizkušanj z antagonisti TNF je bilo opaženih več primerov malignomov, vključno z limfomi, tako pri bolnikih, ki so prejemali antagonist TNF, kot pri kontrolnih bolnikih. Hematološke reakcije: Pri uporabi antagonistov TNF je bila v redkih primerih opisana pancitopenija, vključno z aplastično anemijo. Kongestivno srčno popuščanje: Pri bolnikih z blagim srčnim popuščanjem je treba Humiro uporabljati previdno. Avtoimunska dogajanja: Zdravljenje lahko povzroči nastanek avtoimunskih protiteles. Operacije: Bolnika, ki med zdravljenjem potrebuje operacijo, je treba natančno nadzirati glede okužb in ustrezno ukrepati. Starejša populacija: Posebna pozornost glede tveganja okužb je potrebana pri zdravljenju starejših.
Medsebojno delovanje z drugimi zdravili in druge oblike interakcij: Če je bila Humira uporabljena skupaj z metotreksatom, je bilo nastajanje protiteles v primerjavi z monoterapijo manjše. Kombinacija Humire in anakinre ter Humire in abatacepta ni priporočljiva.
Nosečnost in dojenje: Za Humiro ni na voljo kliničnih podatkov od nosečnic, ki so bile izpostavljene zdravilu. ženske ne smejo dojiti vsaj pet mesecev po zadnjem zdravljenju s Humiro.
Vpliv na sposobnost vožnje in upravljanja s stroji: Humira ima lahko blag vpliv na sposobnost vožnje in upravljanja s stroji.
Pogostejši neželeni učinki po organskih sistemih so: infekcijske in parazitske bolezni: različne vrste okužb; benigne, maligne in neopredeljene novotvorbe: benigni tumor, karcinom kože; bolezni krvi in limfatičnega sistema: levkopenija, trombocitopenija, levkocitoza; bolezni imunskega sistema: preobčutljivost, alergije; presnovne in prehranske motnje: zvišanje lipidov; psihiatrične motnje: spremembe razpoloženja, anksioznost, nespečnost; bolezni živčevja: glavobol, parestezije, migrena, ishiadičen nevritis; očesne bolezni: motnje vidnega zaznavanja, konjunktivitis; ušesne bolezni, vključno z motnjami labirinta: vertigo; srčne bolezni: tahikardija; žilne bolezni: hipertenzija, zardevanje, hematom; bolezni dihal, prsnega koša in mediastinalnega prostora: kašelj, astma, dispneja; bolezni prebavil: bolečine v trebuhu, navzeja in bruhanje, gastroinestinalna krvavitev, dispepsija, bolezen gastroezofagealnega refluksa, Sjögrenov sindrom; bolezni jeter, žolčnika in žolčevodov: zvišani jetrni encimi; bolezni kože in podkožja: izpuščaj, srbenje, urtikarija, modrice, dermatitis, oniholiza, čezmerno znojenje; bolezni mišično-skeletnega sistema in vezivnega tkiva: mišičnoskeletne bolečine, mišični spazmi; bolezni sečil: hematurija, ledvična okvara; splošne težave in spremembe na mestu aplikacije: reakcija na mestu injiciranja, bolečina v prsih, edemi; preiskave: koagulacija in motnje krvavenja, prisotnost avtoprotiteles; poškodbe in zastrupitve in zapleti pri posegih: slabše celjenje.
Način in režim izdajanja: Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika.
Imetnik dovoljenja za promet: Abbott Laboratories Ltd, Abbott House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, SL6 4XE Velika Britanija.
Datum revizije besedila: 21.02.2011

Literatura:

1. Data on file. Abbott Laboratories
2. Menter A, Tyring SK, Gordon K, et al. Adalimumabtherapy for moderate to severe psoriasis: a randomized, controlled phase III trial. J Am Acad Dermatol. 2008; 58(1):106-115
3. Gordon K; Poulin Y, Gu Y, Sasso EH. Efficacy and safety in patients with psoriasis treated continuously with adalimumab for approximately 3 years. Poster presented at 68th Annual Meeting of American Academy of Dermatology; March 5-9, 2010; Miami, FL

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Podrobni prikaz zdravljenja okuženega dela nohta si lahko ogledate na www.canesnail.si

Skrajšan povzetek glavnih značilnosti zdravila

Ime zdravila: Canespor 10 mg/g krema. **Sestava:** 1 g kreme vsebuje 10 mg bifonazola. **Terapevtske indikacije:** za zdravljenje kožnih mikoz, ki jih povzročajo dermatofiti, kvasovke, plesni in druge glivice (npr. Malassezia furfur) ter okužbe s Corynebacteriumom minutissimum: tinea pedum, tinea manuum, tinea corporis, tinea inguinalis, pityriasis versicolor, površinske kandidoze in eritrazma. **Odmerjanje in način uporabe:** Kremo Canespor uporabljamo enkrat na dan, najbolje zvečer pred spanjem. Na prizadeto kožo nanesemo tanko plast zdravila in ga vtremo. Učinek je trajnejši, če kremo Canespor uporabljamo pravilno in dovolj dolgo. Običajno traja zdravljenje: mikoz na stopalu in med prsti (tinea pedum, tinea pedum interdigitalis) - 3 tedne; mikoz po telesu, rokah in v kožnih gubah (tinea corporis, tinea manuum, tinea inguinalis) – 2 do 3 tedne; okužb rožene plasti kože, blagih, kroničnih, površinskih okužb (pityriasis versicolor, eritrazma) – 2 tedna; površinskih kandidoz kože – 2 do 4 tedne. Za površino v velikosti dlani zadostuje večinoma že majhna količina kreme. Otroci: Pregled kliničnih podatkov kaže, da uporaba bifonazola pri otrocih ne povzroča škodljivih učinkov. Kljub temu naj se bifonazol pri dojenčkih uporablja le pod zdravniškim nadzorom. **Kontraindikacije:** Preobčutljivost za bifonazol, cetil in stearilalkohol ali katerokoli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Bolniki z anamnezo preobčutljivostnih reakcij na druge imidazolske antimikotike (npr. ekonazol, klotrimazol, mikonazol) morajo previdno uporabljati zdravila, ki vsebujejo bifonazol. Paziti je treba, da zdravilo ne pride v stik z očmi. Krema Canespor vsebuje cetil in stearilalkohol, ki lahko povzroči lokalne kožne reakcije (npr. kontaktni dermatitis). Pri bolnikih, ki so preobčutljivi za cetil in stearilalkohol, je priporočljivo, da namesto kreme Canespor uporabljajo raztopino Mycospor. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Ni podatkov o medsebojnem delovanju z drugimi zdravili. **Nosečnost in dojenje:** Prve 3 mesece nosečnosti smejo ženske bifonazol uporabiti šele potem, ko zdravnik oceni razmerje koristi in tveganja. Dojenje: Ni znano, ali se bifonazol pri človeku izloča v materinem mleku. Doječe matere smejo bifonazol uporabiti šele potem, ko zdravnik oceni razmerje koristi in tveganja. Med obdobjem dojenja ženska bifonazola ne sme uporabljati v predelu prsi. Plodnost: Predklinične študije niso pokazale, da bi bifonazol vplival na plodnost samcev ali samic. **Neželeni učinki:** Splošne težave in spremembe na mestu aplikacije: bolečine na mestu uporabe, periferni edemi (na mestu uporabe); bolezni kože in podkožja: kontaktni dermatitis, alergijski dermatitis, eritem, srbenje, izpuščaj, urtikarija, mehur, eksfoliacija kože, ekcem, suha koža, draženje kože, maceracija kože, pekoč občutek na koži. Ti neželeni učinki po prekinitvi zdravljenja izginejo. **Način in režim izdaje:** Izdaja zdravila je brez recepta v lekarnah. **Imetnik dovoljenja za promet:** Bayer d. o. o., Bravničarjeva 13, 1000 Ljubljana. **Datum zadnje revizije:** 20.10.2011. **Datum priprave informacije**: april 2012. **Vse informacije o zdravilu dobite pri Bayer d.o.o.**

Literatura:

1. Canes-Nail; Navodila za uporabo.
2. Canespor krema; Povzetek glavnih značilnosti zdravila.

Samo za strokovno javnost.

Bayer HealthCare

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Advantan®

Metilprednizolon aceponat

BAYER

Brez kompromisov: MOČAN IN DOBRO PRENOSLJIV[1]

- Hitro učinkovanje[2]
- Kratkotrajno zdravljenje[2]
- Odlični terapevtski rezultati[2]
- Dobra prenosljivost[2]
- Od 4. meseca starosti dalje[3]

dermalna emulzija | krema | mazilo

POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila, ki ga dobite pri naših strokovnih sodelavcih ali na sedežu družbe.

Ime zdravila Advantan 1 mg/g krema, Advantan 1 mg/g mazilo. **Kakovostna in količinska sestava** 1 g kreme vsebuje 1 mg metilprednizolonaceponata (MPA). Pomožne snovi: cetil in stearilalkohol (2,5 g/100 g), butilhidroksitoluen E321 (0,006 g/100 g). 1 g mazila vsebuje 1 mg metilprednizolonaceponata (MPA). **Farmacevtska oblika** krema, bela krema, mazilo, belo do rahlo rumeno mazilo. **Terapevtske indikacije** Atopični dermatitis (endogeni ekcem, nevrodermitis), kontaktni ekcem, degenerativni, dishidrotični, vulgarni ekcem, ekcem pri otrocih. **Odmerjanje in način uporabe** Na splošno je potrebno zdravilo Advantan glede na prizadete predele nanesti v tanki plasti enkrat na dan in rahlo vtreti. Na splošno naj odrasli zdravila ne uporabljajo dlje kot 12 tednov, otroci pa ne dlje kot 4 tedne. **Kontraindikacije** Tuberkuloza ali sifilitični procesi na področju, ki ga je treba zdraviti; virusne bolezni (npr. norice, herpes zoster), rozacea, perioralni dermatitis, postvakcinacijske kožne reakcije v predelu potrebnem zdravljenja. Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. **Posebna opozorila in previdnostni ukrepi** Dodatno specifično zdravljenje je potrebno pri bakterijskih in/ali glivičnih okužbah. Če zdravilo Advantan krema po daljši uporabi kožo preveč izsuši, je treba preiti na eno od oblik, ki vsebujejo več maščob (Advantan mazilo). Pri nanašanju na kožo obraza je treba paziti, da zdravilo Advantan ne pride v oči. Doslej niso opazili, da bi zdravilo Advantan prizadelo adrenokortikalno funkcijo - ne pri odraslih ne pri otrocih, niti pri uporabi na velikih površinah (40 – 60 % telesne površine) niti pod okluzijo. Kljub temu pa je treba zdravilo Advantan pri zdravljenju velikih površin uporabljati čim krajši čas. Uporaba kortikoidov za lokalno uporabo na velikih površinah telesa ali pri dolgotrajni uporabi še posebej pod okluzijo, pomembno poveča tveganje za neželene učinke. Kot je znano pri sistemskih kortikoidih se lahko tudi pri lokalno uporabljenih kortikoidih (npr. pri velikih odmerkih ali pri dolgotrajni uporabi, pri uporabi pod okluzijo ali na koži okoli oči) razvije glaukom. Zdravilo Advantan 1 mg/g krema vsebuje cetil in stearilalkohol ter butilhidroksitoluen (E321), zato lahko povzroči lokalne kožne reakcije (npr. kontaktni dermatitis) ali draženje oči in mukoznih membran. **Nosečnost in dojenje** Na splošno se je treba v prvem trimesečju nosečnosti izogibati lokalnim pripravkom, ki vsebujejo kortikoide. Pri terapevtskih indikacijah za zdravljenje z zdravilom Advantan je treba skrbno pretehtati koristi in tveganja med nosečnostjo in dojenjem. Še posebej se je treba izogibati zdravljenju velikih predelov ali dolgotrajni uporabi. Doječe matere naj zdravila ne aplicirajo na dojke. **Neželeni učinki** V posameznih primerih se pri zdravljenju z zdravilom Advantan lahko pojavijo neželeni učinki, kot so srbenje, pekoč občutek, eritem ali vezikulacija. Naslednji neželeni učinki se lahko pojavijo, če se pripravki za lokalno uporabo, ki vsebujejo kortikoide uporabljajo na velikih površinah telesa (okoli 10 % in več) ali pri dolgotrajni uporabi (več kot 4 tedne): lokalni simptomi kot atrofija kože, teleangiektazije, strije, aknam podobne spremembe kože in sistemski učinki kortikoidov zaradi absorpcije. Med kliničnimi preskušanji se navedeni neželeni učinki niso pojavljali pri uporabi zdravila Advantan do 12 tednov (odrasli) in 4 tednov (otroci). Kot pri drugih kortikoidih za lokalno uporabo se v redkih primerih pojavijo še naslednji neželeni učinki: folikulitis, hipertrihoza, perioralni dermatitis, razbarvanje kože, alergijske reakcije na koži na katerokoli sestavino zdravila. **Imetnik dovoljenja za promet** Intendis GmbH Berlin, Max-Dohrn-Strasse 10, 10589 Berlin, Nemčija **Datum zadnje revizije besedila** 14.4.2011.

Ime zdravila Advantan 1 mg/g dermalna emulzija. **Kakovostna in količinska sestava** 1 g dermalne emulzije vsebuje 1 mg metilprednizolonaceponata. Pomožne snovi: srednjeverižni nasičeni trigliceridi, kaprilo-kaprino-stearinski trigliceridi, polioksietilen-(2)-stearilalkohol, polioksietilen-(21)-stearilalkohol, benzilalkohol, natrijev edetat, 85 odstotni glicerol, prečiščena voda. **Farmacevtska oblika** Dermalna emulzija, oljna in vodna emulzija, bela motna. **Terapevtske indikacije** Blag do zmeren akutni eksogeni ekcem (alergijski kontaktni dermatitis, iritantni kontaktni dermatitis, numularni (mikrobni) ekcem, dishidroza, navadni ekcem) in endogeni ekcem (atopijski dermatitis, nevrodermitis), hujše oblike seboroičnega dermatitisa. **Odmerjanje in način uporabe** Zdravilo Advantan 1 mg/g dermalna emulzija je potrebno na prizadete predele nanesti v tanki plasti enkrat na dan in rahlo vtreti. Pri odraslih zdravila naj ne bi uporabljali dlje kot 2 tedna. V primeru hujših oblik seboroičnega dermatitisa se prizadetih delov obraza ne sme zdraviti dlje kot en teden. Pri otrocih mora zdravljenje trajati čim krajši čas.Če se koža med uporabo zdravila Advantan 1 mg/g dermalna emulzija pretirano izsuši, je glede na bolnikov tip kože priporočljivo uporabiti dodatno nevtralno zdravljenje (emulzijo V/O ali enofazno maščobno mazilo). **Kontraindikacije** preobčutljivost za zdravilno učinkovino ali katerokoli od pomožnih snovi, tuberkulozne ali sifilitične spremembe, virusne okužbe (npr. herpes ali norice), rozacea, perioralni dermatitis, razjede, navadne akne, atrofične bolezni kože, povakcinacijske kožne reakcije na predelu, ki ga je potrebno zdraviti. Zdravila Advantan 1 mg/g dermalna emulzija se ne sme nanašati na oči in odprte rane. V prvem trimesečju nosečnosti se zdravilo Advantan 1 mg/g dermalna emulzija ne sme aplicirati na več kot 20 % kožne površine. Zaradi pomanjkanja izkušenj je uporaba kontraindicirana pri otrocih do 4. meseca starosti. Pri starejših otrocih, npr. dojenčkih po 4. mesecu in malih otrocih do 3 let, je treba skrbno oceniti razmerje med koristjo in tveganjem. Bakterijske in glivične kožne bolezni. **Posebna opozorila in previdnostni ukrepi** Glukokortikoidi naj se uporabljajo v čim manjšem odmerku, še posebej pri otrocih, in le toliko časa kot je nujno potrebno za dosego in vzdrževanje željenega terapevtskega učinka. V primeru bakterijskih kožnih bolezni in/ali glivičnih okužb je potrebno dodatno specifično zdravljenje. Lokalna uporaba glukokortikoidov lahko poslabša lokalne okužbe na koži. Med uporabo zdravila Advantan 1 mg/g dermalna emulzija je treba paziti, da ne pride v stik z očmi, odprtimi ranami in sluznicami. Zdravila Advantan 1 mg/g dermalna emulzija se ne sme uporabljati za zdravljenje velikih površin kože (več kot 40 % kožne površine). Zdravilo Advantan 1 mg/g dermalna emulzija se ne sme uporabljati na intertriginoznih predelih. Pri zdravljenju obsežnih predelov (40 – 60 % kožne površine) z zdravilom Advantan 1 mg/g dermalna emulzija doslej niso opazili motenj adrenokortikalnega delovanja niti pri odraslih niti pri otrocih in tudi ne pod nepropustnim povojem. Kljub temu se zdravilo Advantan 1 mg/g dermalna emulzija ne sme uporabljati pod nepropustnimi (okluzivnimi) povoji. Previdnost je potrebna pri uporabi plenic, ker lahko delujejo okluzivno. Uporaba kortikosteroidov za lokalno uporabo na velikih površinah telesa ali dolgotrajna uporaba , posebno pod nepropustnim povojem, pomembno poveča tveganje za pojav neželenih učinkov. Pri zdravljenju velikih površin kože, še zlasti med nosečnostjo in dojenjem, mora zdravljenje trajati čim krajši čas, ker ni mogoče povsem izključiti absorpcije in sistemskega učinka. Kot velja za vse glukokortikoide, lahko nestrokovna uporaba prikrije klinične simptome. Zdravilo lahko vsebuje stearilalkohol, ki lahko povzroči lokalne kožne reakcije (npr. kontaktni dermatitis). Nosečnost in dojenje: O uporabi zdravila Advantan 1 mg/g dermalna emulzija pri nosečnicah ni dovolj podatkov. Pred uporabo zdravila Advantan 1 mg/g dermalna emulzija med nosečnostjo ali dojenjem skrbno pretehtati koristi in tveganje. Na splošno se je treba v prvem trimesečju nosečnosti izogibati lokalnim pripravkom, ki vsebujejo kortikoide. Med nosečnostjo in dojenjem se je zlasti treba izogibati zdravljenju velikih površin kože, dolgotrajni uporabi in nepropustnim povojem. Doječe matere naj zdravila ne aplicirajo na dojke. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij** Zaradi absorpcije lahko zdravljenje na velikih površinah kože ali dolgotrajno zdravljenje povzroči podobne interakcije, kot se pojavijo pri sistemskem zdravljenju. Doslej ni znanih medsebojnih delovanj z drugimi zdravili. **Neželeni učinki** Občasno lahko zdravilo Advantan 1 mg/g dermalna emulzija povzroči blago draženje kože, npr. blag in prehoden pekoč občutek. Redkeje se pojavijo srbenje, eritem, suha koža, luščenje in folikulitis. Preobčutljivostne reakcije na sestavine. Čeprav tega v kliničnih preskušanjih doslej niso ugotavljali, lahko lokalna uporaba steroidov zlasti med dolgotrajno uporabo povzroči atrofijo kože, teleangiektazije, strije in/ali akne. Kot velja za vse glukokortikoide se lahko, čeprav redko, pojavijo folikulitis, hipertrihoza, perioralni dermatitis, alergijski kontaktni dermatitis, depigmentacije (razbarvanje kože) in sistemsko delovanje. **Imetnik dovoljenja za promet** Intendis GmbH Berlin, Max-Dohrn-Strasse 10, 10589 Berlin, Nemčija **Datum zadnje revizije besedila** 13.3.2009

Reference: 1 Zaumseil R-P, Fuhrmann H, Kecskés A, et al. Methylprednisolone aceponate (Advantan®) – an effective topical corticoid therapy with few side effects; Jahrbuch der Dermatologie 1992; 93: 247–263. **2** Bieber T, et al. Efficacy and safety of methylprednisolone aceponate ointment 0.1 % compared to tacrolimus 0.03 % in children and adolescents with an acute flare of severe atopic dermatitis. Allergy 2007; 62: 184–9. **3** Povzetek glavnih značilnosti zdravila Advantan dermalna emulzija.

Samo za strokovno javnost.

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