Miescher's granulomatosis (granulomatosis disciformis chronica et progressiva) in a non-diabetic patient – case report

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Abstract

Introduction: Necrobiosis lipoidica diabeticorum is a rare disease of unclear etiology, that occurs in about 1% of diabetic patients [1]. The disease is characterized by a chronic inflammatory granulomatous process accompanied by vasculitis with perivascular deposits of complement C3 and immunoglobulins IgG, IgM and IgA. Typically found on the lower legs, focal skin lesions comprise well-separated irregular areas of discolored (yellow-brown) tissue. Tissue damage in the centre of foci includes atrophy, sclerosis and telangiectasia [1-3].

Miescher's granulomatosis (also known as granulomatosis disciformis chronica et progressiva) was first reported by Miescher and Leder in 1948. In this condition skin lesions are typically localized bilaterally and symmetrically on the lower legs, and in the absence of diabetes [1,4]. Treatment of all types of necrobiosis lipoidica is difficult, and the condition can be unresponsive to systemic corticosteroids, cyclosporin A, retinoids, and antimalarial and vascular drugs. In contrast, some promising results have been obtained with phototherapy (psoralen and UVA treatment; PUVA), with topical application of corti-
costeroids or tacrolimus, or with photodynamic therapy [5-11].

We present a case of Miescher’s granulomatosis without diabetes showing a favorable response to systemic corticosteroid therapy.

**Case report**
The patient (female, 45 yr) had primary skin lesions consisting of discolored (yellow-brown) areas on both lower legs with well-separated foci (Fig. 1). Her condition was first reported 5 years earlier. The initial diagnosis was erythema induratum, and treatment included penicillin G procaine, rifampicin, vascular drugs and local steroidotherapy. Diagnosis of Miescher’s granulomatosis was suggested 3 years later on the basis of histopathologic examination and after exclusion of diabetes. We repeated penicillin G procaine, vascular drug administration and steroidotherapy. Cryotherapy with ethyl chloride was also applied. Despite the treatment the extent of the skin lesions increased slowly and these were accompanied by small ulcerations within the lesion foci, often as a result of local injury.

Thyroid disease was diagnosed in 2007 (Hashimoto’s thyroiditis, struma nodosa partim lymphomatosa Hashimoto) and subtotal resection of the thyroid gland was performed. Thyroid hormone replacement was with Eltroxin (levothyroxine, 100 mg). In the same year the patient was hospitalized in a provincial dermatological ward where a diagnosis of xanthogranuloma necrobioticum was suggested. Because treatment brought no improvement, and the extent of the skin lesions continued to increase, the patient was admitted to Department of Dermatology at Katowice Medical University.

Laboratory investigations included ESR 32/52, blood smear, electrolyte levels, AspAT, ALAT, GGTP, bilirubin, creatinine, urea, glucose, blood glucose profile, blood protein electrophoresis, CPK, aldolase, urine analysis, arthus-type reactions (latex-R, Waaler-Rose test, ASO). All were in the normal range. Because xanthogranuloma necrobioticum had been suggested tests for paraproteinemias were also performed. Immuno electrophoresis revealed normal levels of IgG, IgM, IgA, kappa light chain, and lambda heavy chain; there was no evidence of Bence-Jones proteins.

In therapy methylprednisolone (32 mg od) was administered in conjunction with vascular drugs and local steroidotherapy. After 1 month of methylprednisolone there was significant improvement, with flattening and blanching of skin lesions accompanied by healing of minor ulcerations on the left lower leg. The patient is now receiving dermatologic out-patient care with continued administration of methylprednisolone and gradual dose reduction (table 1).

**Discussion**
Necrobiosis lipoidica in its classical form is a granulomatous disease of unclear etiology usually associated with diabetes. Ho et al. [12] reported on an atypical familial case where necrobiosis lipoidica without diabetes was found in 2 sisters. Flann et al. [13] and Criado et al. [14] described many histological similarities between the progression of xanthogranuloma necrobioticum and Miescher’s granulomatosis, although the overall clinical picture differs between the two conditions. Leroy et al. [15] performed electron microscope ultrastructural studies in a patient (62 yr) with a diagnosis of necrobiosis lipoidica without diabetes. Here perivascular macrophage infiltration, necrobiosis and collagen fiber damage was reported but without loss of vascular wall integrity.

Treatment of classical variants of necrobiosis lipoidica and Miescher’s granulomatosis is difficult. Bawaria et al. [16] applied pentoxifylline (3 × 400 mg td) in a 20-yr-old patient with diabetes and necrobiosis lipoidica. Tan et al. [17] used systemic corticosteroid with success in patients with necrobiosis lipoidica and insulin-dependent diabetes, and without destabilization of blood glucose levels. In our patient, long-term topical corticosteroid therapy gave no detectable clinical improvement.

Narbutt et al. [10] used local PUVA therapy (0.005% 8-methoxypsoralen followed by UVA irradiation) in 10 patients. After an average of 47 sessions (total dose 69.5 J/cm²) they observed recurrence of skin lesions in only 2
patients. Kreuter et al. [18] used fumaric acid esters (FAE) for the therapy of necrobiosis lipoidica, granuloma annulare and a skin variant of sarcoidosis. In 18 necrobiosis patients receiving FAE over 6 mo there was a significant improvement in skin status.

Bouhanick et al. [19] complemented steroid therapy with 113 sessions in hyperbaric chamber. This joint therapy was effective in a patient (28 yr) with insulin-dependent diabetes. Reinhard et al. [20] obtained good results in necrobiosis lipidica treatment using mycophenolate mofetil. Nguyen et al. [21] described an individual case of therapeutic success in a patient with necrobiosis after administration of an antimalarial drug (chloroquine). Owen et al. [22] reported a case of a 44-yr-old woman with ulcerated necrobiosis lipidica that healed following grafting with dermal tissue engineered in culture. Zeichner et al. [23] treated necrobiosis lipidica using a TNF inhibitor (etanercept).

Long-term risks associated with necrobiosis lipidica include the development of spinocellular carcinoma. Tschuchnigg et al. [24] detected nodules within the necrobiosis foci in a 53-yr-old patient; these were diagnosed histologically as spinocellular carcinoma. Santos-Juanes et al. [25] made similar observations in a 75-yr-old patient with a 30 yr history of necrobiosis lipidica.

Conclusion
We have described a case with typical clinical and histological features of necrobiosis lipidica in the absence of diabetes, also known as Miescher’s granulomatosis. Treatment of this type of necrobiosis is difficult, and the condition failed to respond to different attempts at therapy over several years. We report that systemic steroidotherapy with methylprednisolone was of significant clinical benefit in this patient. Early diagnosis and treatment can not only improve the patient’s quality of life but also protect against serious side-effects including spinocellular carcinoma.

Consent
We confirm that written consent was obtained from the patient or their relatives for publication of study and the use of any images. A copy of the written consent is available for review by the Editor-in-Chief of this Journal.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
This manuscript was drafted by BBC, LBW, IRP. BBC – main conception, design, acquisition of data, interpretation of data, writing; LBW – references, writing assistance; IRP – writing assistance, acquisition of data. All authors contributed to its critical review and all approved the final draft.

References
1. Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC. Necrobiosis lipidica. Dermatology, Czelej, Lublin 2002:1305-1306.
2. Almond-Roesler B, Ramaker J, Dippel E, Blume-Peytavi U, Goerdt S. Granulomatosis disciformis Miescher. Hautarzt 1998, 49:228-230.
3. Császár A, Daróczy J, Szénási P, Anda L, Tóth L, Hosszúfalusi N, Karádi I, Kalabay L, Romics L. Necrobiosis lipidica without diabetes mellitus (diagnostic and therapeutic possibilities). Orv Hetil 1989, 130:2141-2145.
4. Peyri J, Moreno A, Marcová J. Necrobiosis lipidica. Semin Cutan Med Surg 2007, 26:87-89.
5. Aslan E, Korber A, Grabbe S, Dissemend J: Successful therapy of ulcerated necrobiosis lipidica non diabeticorum with cyclosporine A. Hautarzt 2007, 58:684-688.
6. Beattie PE, Dawe RS, Ilbottson SH, Ferguson J. UVA1 phototherapy for treatment of necrobiosis lipidica. Clin Exp Dermatol 2006, 31:235-238.
7. Boyd AS. Tretinoin treatment of necrobiosis lipidica diabeticorum. Diabetes Care 1999, 22:1753-1754.

Table 1: Clinical history of the patient

| date  | disease                     | lab results          | therapy                                      | result (skin) |
|-------|-----------------------------|----------------------|----------------------------------------------|---------------|
| 2002  | erythema induratum (?)      | normal range         | penicillin G procaine, rifampicin, vascular  | stable        |
|       |                             |                      | drugs, local steroidotherapy                 |               |
| 2005  | Miescher’s granulomatosis   | histopathologic      | penicillin G                                 | stable        |
|       |                             | examination – Miescher’s granulomatosis |                      |               |
| 2007  | Hashimoto’s thyroiditis     | Anty-TPO antibodies – high range, T3, T4 – low range, TSH – high range, ultrasonography, histopathologic examination – Hashimoto’s thyroiditis | subtotal resection of the thyroid gland | stable        |
|       |                             |                      | Ertroxin (levothyroxine, 100 mg)              |               |
| 2007  | xanthogranuloma necrobioticum (?) | normal range        | micromolecular heparin vascular drugs         | deterioration |
| 2007  | Miescher’s granulomatosis   | ESR 32/52, the rest – normal range | methylprednisolone (32 mg od)                 | improvement   |
8. Clayton TH, Harrison PV: Successful treatment of chronic ulcerated necrobiosis lipoidica with 0.1% topical tacrolimus ointment. Br J Dermatol 2005, 152:581-582.

9. Heideheimein M, Jemer G: Successful treatment of necrobiosis lipoidica diabeticorum with photodynamic therapy. Arch Dermatol 2006, 142:1548-1550.

10. Narbutt J, Torzecka JD, Sysa-Jedrzejowska A, Zalewska A: Long-term results of topical PUVA in necrobiosis lipoidica. Clin Exp Dermatol 2006, 31:65-67.

11. Taniguchi Y, Sakamoto T, Shimizu M: A case of necrobiosis lipoidica treated with systemic corticosteroid. J Dermatol 1993, 20:304-307.

12. Ho KK, O’Loughlin S, Powell FC: Familial non-diabetic necrobiosis lipoidica. Australas J Dermatol 1992, 33:31-34.

13. Flann S, Wain EM, Halpern S, Andrews V, Whittaker S: Necrobiotic xanthogranuloma with paraproteinaemia. Clin Exp Dermatol 2006, 31:248-251.

14. Criado PR, Vasconcellos C, Pegas JR, Lopes LF, Ramos CF, Tebcherani AJ, Valente NY: Necrobiotic xanthogranuloma with lambda paraproteinaemia: case report of successful treatment with melphalan and prednisone. J Dermatolog Treat 2002, 13:87-89.

15. Leroy JP, Peu-Duvallon P, Bruch JF, Boudon A, Guillou AM, Volant A: Ultrastructural study of a case of Miescher-Leder granulomatosis disciformis chronica et progressiva. Ann Dermatol Venereol 1985, 112:433-439.

16. Basaria S, Braga-Basaria M: Necrobiosis lipoidica diabeticorum: response to pentoxifylline. J Endocrinol Invest 2003, 26:1037-1040.

17. Tan E, Patel V, Berth-Jones J: Systemic corticosteroids for the outpatient treatment of necrobiosis lipoidica in a diabetic patient. J Dermatolog Treat 2007, 18:246-248.

18. Kreuter A, Krierim C, Stucke M, Pawlak F, Rotterdam S, Altmeyer P, Gambichler T: Fumaric acid esters in necrobiosis lipoidica: results of a prospective noncontrolled study. Br J Dermatol 2005, 153:802-807.

19. Bouhanick B, Verret JL, Gouello JP, Berrut G, Marre M: Necrobiosis lipoidica: treatment by hyperbaric oxygen and local corticosteroids. Diabetes Metab 1998, 24:156-159.

20. Reinhard G, Lohmann F, Uerlich M, Bauer R, Bieber T: Successful treatment of ulcerated necrobiosis lipoidica with mycophenolate mofetil. Acta Derm Venereol 2000, 80:312-313.

21. Nguyen K, Washenik K, Shupack J: Necrobiosis lipoidica diabeticorum treated with chloroquine. J Am Acad Dermatol 2002, 46:34-36.

22. Owen CM, Murphy H, Yates VM: Tissue-engineered dermal skin grafting in the treatment of ulcerated necrobiosis lipoidica. Clin Exp Dermatol 2001, 26:176-178.

23. Zeichner JA, Stern DW, Lebwohl M: Treatment of necrobiosis lipoidica with the tumor necrosis factor antagonist etanercept. J Am Acad Dermatol 2006, 54:120-121.

24. Tschuchnigg M, Lim J: Squamous cell carcinoma arising in an area of long-standing necrobiosis lipoidica. J Cutan Pathol 2006, 33:581-583.

25. Santos-Juans J, Gañache C, Curto JR, Carrasco MP, Ribas A, Sánchez del Rio J: Squamous cell carcinoma arising in long-standing necrobiosis lipoidica. J Eur Acad Dermatol Venereol 2004, 18:199-200.