Lesioni infiammatorie e neoplastiche della cute
Roma, 10-11 Aprile 2017

Casi clinici rari ed inusuali:
Correlazioni clinico-patologiche

Lorenzo Cerroni
Further history and investigations

- Increasing oedema and erythema of the eyelids since April 2016; no other complains
- First presentation to ophtalmologist in June; cutaneous biopsy
- ANA 1:640; MDA5 60 (0-10); DIF negative (3x)
- July: Erythematous changes on decollete, hands; muscle pain; treatment with hydrochloroquine
- August: elevated liver enzymes, respiratory insufficiency
- September: interstitial pneumonia
- Rapid progression; exitus September 19, 2016
MDA5+ dermatomyositis

- A variant of DM that can be associated with interstitial lung disease carrying a potentially severe prognosis
- Some patients have amyopatic disease
- Onset may be subtle; sometimes overlapping clinicopathological features with LE
- Careful monitoring of the patients for the development of lung involvement
- Patients with elevated ferritin levels (>1600 ng/ml) may have a worse prognosis
Clinical manifestation and prognostic factor in anti-melanoma differentiation-associated gene 5 antibody-associated interstitial lung disease as a complication of dermatomyositis

Takahisa Gono, Yasushi Kawaguchi, Takashi Satoh, Masatake Kuwara, Yasuohiro Katsuma, Kae Takagi, Ikuko Masuda, Aiko Tochimoto, Sayumi Baba, Yuko Okamoto, Yuko Ota, and Hisashi Yamanaka

Abstract

Objective. The aim of this study is to evaluate the clinical manifestation and prognostic factors of anti-melanoma differentiation-associated gene 5 (MDA5) antibody-associated interstitial lung disease (ILD) with DM.

Methods. Fourteen patients who presented with anti-MDA5 antibody and 10 patients with anti-Kalirai-7 anti-RNA synthetase (ARS) antibody were enrolled. All patients were diagnosed as having DM with ILD. Clinical manifestations in the patients with anti-MDA5 antibody were compared with those in the patients with anti-ARS antibody.

Results. The frequency of aspergillosis-associated interstitial pneumonia (ASIP) and fatal outcome were significantly higher in the subset with anti-MDA5 antibody. The creatinine kinase (CK) value was significantly lower and the γ-glutamyl transpeptidase and ferritin values were significantly higher in the subset with anti-MDA5 antibody. Significant correlations were found between PaO₂/FiO₂ and ferritin (r = -0.39, P = 0.039, alveolar-arterial oxygen difference (A-aDO₂) and CK (r = 0.73, P = 0.039) and A-aDO₂ and ferritin (r = 0.66, P = 0.015) in the subset with anti-MDA5 antibody. The most significant prognostic factor was ferritin. The cumulative survival rate was significantly lower (P = 0.0001) in the subset with ferritin >1600 ng/ml than that in the subset with ferritin <1600 ng/ml in anti-MDA5 antibody-associated ILD.

Conclusion. Both serum ferritin and anti-MDA5 antibody are powerful indicators for the early diagnosis of ASIP with DM. Ferritin also predicts disease severity and prognosis for patients with anti-MDA5 antibody. Intensive treatment should be administered to cases that have anti-MDA5 antibody-associated ILD with DM showing hyperferritinemia, especially if the ferritin level is >1600 ng/ml.

Key words: Dermatomyositis, Interstitial lung disease, Melanoma differentiation-associated gene 5, Ferritin, MicroRNA activation.

Introduction

DM is characterized by inflammation of the skin and muscles (1). DM is occasionally complicated with interstitial lung disease (ILD), which is classified into two subsets: aspergillosis-associated interstitial pneumonia (ASIP) and chronic interstitial pneumonia (CIP). In ASIP, ILD is a prime importance in the clinical management of patients with DM because it is an infiltrative and infiltrating condition (2, 3). Clinically, DM (C-ADM) includes typical skin lesions with amyopathic dermatomyositis (4, 5). Clinically, DM (C-ADM) includes typical skin lesions and amyopathic dermatomyositis (4, 5). Clinically, DM (C-ADM) includes typical skin lesions and amyopathic dermatomyositis (4, 5). Clinically, DM (C-ADM) includes typical skin lesions and amyopathic dermatomyositis (4, 5). Clinically, DM (C-ADM) includes typical skin lesions and amyopathic dermatomyositis (4, 5). Clinically, DM (C-ADM) includes typical skin lesions and amyopathic dermatomyositis (4, 5). Clinically, DM (C-ADM) includes typical skin lesions and amyopathic dermatomyositis (4, 5).

In the patient from Graz 58x blood investigations within 79 days, yet ferritin levels never checked.
Further history and investigations

- $\alpha_1$ antitrypsine 0,25 g/l (0,9 – 2,6); genotype ZZ
- 1st diagnosis in 1993 at the age of 16 years
- At the age of 39 onset of the new lesions at the same site as the ones observed >20 years before (at that time therapy with dapsone)
- Marked improvement after 2x prolastin ($\alpha_1$-proteinase inhibitor)
α1-antitrypsine deficiency panniculitis

• **SERPINA1** gene mutations. Normal production: allele M; allele S produces moderately low levels; allele Z produces very low levels
• Worldwide, it is estimated that 161 million people have one copy of the S or Z allele and one of the M allele (MS or MZ genotype); those with MZ alleles have a slightly increased risk of impaired lung or liver function
• Chronic obstructive lung disease, impaired liver function (leading cause of liver transplantation in newborns), panniculitis
• Estimated prevalence of panniculitis is 1 in 1000 subjects with severe α1ATD (usually white individuals with ZZ genotype)
Neutrophilic panniculitis associated with alpha-1-antitrypsin deficiency: an update

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Summary

Neutrophilic panniculitis associated with alpha-1-antitrypsin deficiency (AATD) is a very rare disease. Its estimated prevalence in 1 in 1000 subjects with severe AATD (usually white individuals with a PiZ allele) is a condition characterized by painful, recurrent, subcutaneous, subcutaneous nodules and abscesses that may be associated with neutrophils in the deep dermis and subcutaneous tissue, with necrotizing nodular panniculitis. It may be the only clinical manifestation of AATD, although it may also occur together with the clinical presentation of other manifestations of the disease. AATD-associated panniculitis is not only very rare but may also be significantly underestimated. The physician managing a case of panniculitis with a clinical presentation suggestive of AATD should be aware of the need to screen for AAT deficiency and, if necessary, obtain the AAT genotype by routine testing. Familiarity with the AATD genome should be extended to identify the genotype. If AAT is found to be deficient, AATD testing of non-affected family members should be performed in order to take appropriate preventive and therapeutic measures, including genetic counseling, education on avoidance of tobacco and occupational exposure to asbestos and low-density lipoprotein, and the provision of information on clinical management. This is particularly important in cases where conventional therapy with corticosteroids and other immunosuppressive agents has failed. The current consensus is that the diagnosis of neutrophilic panniculitis should be made with a high level of confidence. The current consensus is that the diagnosis of neutrophilic panniculitis should be made with a high level of confidence and that the diagnosis should be made with a high level of confidence.
Further history and investigations

• Pancreas transplantation 1994
• Known SLE (1st diagnosis 1995)
• Lupus nephritis
• Renal Tx 2000, explantation 2007, new renal Tx 2009
• Verrucous lesions on the lower extremities slowly growing for the last 3 years
Verrucous porokeratosis

- A variant of porokeratosis characterized by a florid epithelial hyperplasia
- Oft in the setting of porokeratosis ptychotropica
- May mimic psoriasis, lichen simplex chronicus
- At least in some cases it may represent LSC superimposed on conventional porokeratosis
Verrukose Variante der Porokeratosis Mibelli als Differenzialdiagnose der Psoriasis vulgaris

Die Porokeratosen stellen eine heterogene Gruppe von Dermatosen dar, die pathogenetisch auf einer Störung der Keratinozyten rekonstruktiver Verfassungsformen im Bereich der Hornschicht basieren. Die Porokeratose Mibelli ist eine röntgenologisch charakteristische Form mit Verhornungshypertrophie, die durch die pathologische Keratinisierung und Verhornung der Mitosen charakterisiert ist. Die Porokeratose Mibelli ist durch eine erythematöse, meist multipolare Verhornung charakterisiert.

Kasuistik

Anamnese


Abbildung 1: Ausgedehnte Verhornungshypertrophie auf der Rückenpartie

Abbildung 2: Detailansicht der Verhornungshypertrophie

Abbildung 3: Biopsie von der Verhornungshypertrophie

Die Diagnose der Porokeratose Mibelli wurde durch eine histologische Untersuchung der Biopsie gesichert, die eine charakteristische Verhornungshypertrophie mit Ausbildung von Keratinozytenhypertrophie und Verhornungshypertrophie zeigte. Die Therapie der Wahl ist die topische Therapie mit Retinoiden oder systemische Therapie mit Immunsuppressiva, je nach Schweregrad der Erkrankung.
Further history and investigations

- Known SLE (1\textsuperscript{st} diagnosis: \textasciitilde20a before)
- Several previous treatments (resochin, plaquenil, dapsone, MTX, imurek, thalidomide, aprednislone, quensyl); at present no treatment
- New verrucous lesions on the skin for the last few weeks/months
- ANA 1:1280; ENA 22.0; Ro-Abs 211.0; Ro52-Abs 26.0; Ro60-Abs 242.0
Verrucous lupus erythematous

- A variant of cutaneous LE characterized by verrucous lesions simulating an epithelial tumor
- May be misinterpreted as multiple eruptive keratoacanthomas clinically, and as SCC histologically (particularly on superficial biopsies)
- SCC is an uncommon, late complication of verrucous LE
- LE hypertrophicus et profundus is a rare destructive variant of verrucous LE with eventual subcutaneous necrosis
### Variants of lupus erythematosus

- LE tumidus / Jessner-Kanof
- LE profundus (panniculitis)
- Neonatal LE
- Chilblain LE
- Multiforme-like LE - Rowell syndrome / Toxic epidermal necrolysis-like eruption of ACLE (acute syndrome of apoptotic pan-epidermolysis (ASAP)
- Bullous LE
- Drug-induced LE
- Paraneoplastic LE
- Linear LE
- Neutrophilic dermatitis in LE
- **Verrucous LE**
- Follicular LE
- Acrosyringeal LE
- Alopecia in LE
- Mucosal involvement in LE
- Interstitial granulomatous dermatitis in LE
- Papulonodular LE with diffuse mucin deposition
- SLE / scleroderma overlap syndrome
- LE / lichen planus overlap syndrome
- Pseudolymphomatous LE (several variants)
- ? REM
- ? Degos disease (malignant atrophic papulosis)
- ? Equestrian chilblain (cold "panniculitis")
Further history and investigations

• Since 3 months erosive lesions on the scalp; diagnosis of gingivo-stomatitis herpetica made at the HNO department; no improvement with antibiotics and valacyclovir + acyclovir
• DIF: IgG and C3 intraepidermal
• Desmoglein 1: 127 (0-20)
  Desmoglein 3: 154 (0-20)
Pemphigus vulgaris in young patients

• Mean age of onset 50-60
• A few cases reported in childhood *(fogo selvagem is a disease of young adults and children)*
• Clinicopathological features similar to those of adult pemphigus
Further history and investigations

- Recent excision of a malignant melanoma on the left thigh (Breslow 3,3 mm)
- Admitted as in-patient for re-excision and sentinel lymph node biopsy (positive, 6/10 positive LNs upon dissection)
- Prophylactic heparin treatment
- Sudden onset of haemorrhagic bullae at sites distant from the injection
- Six months later lung metastases
Hemorrhagic bullae after heparin injection

- Rare complication observed with different types of heparin at sites distant from the injection site
- Intraepidermal / subcorneal hemorrhagic blister with angiokeratoma-like pattern, but absence of true vessels
- Mechanism of blister formation unclear; hypersensitivity reaction unlikely (eosinophils found only in 1/19 cases in which biopsy examination was performed)
Bullous hemorrhagic dermatosis occurring at sites distant from subcutaneous injections of heparin: Three cases

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Cutaneous side effects from heparin administration are rare and usually located at injection sites. We report 3 cases of intraperiostal hemorrhagic blisters occurring distant from sites of subcutaneous injections of heparin. A causative link is suggested by a temporal relationship between heparin introduction and onset of disease as well as exclusion of other causes, but the mechanism remains unknown. (J Am Acad Dermatol 2005;54:55-7.)

Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are associated with few cutaneous side effects except for local reactions to subcutaneous injections, including hematoma, skin necrosis, contact dermatitis, and urticaria. Skin necrosis is due to thrombosis of dermal capillary vessels and may be related to heparin-platelet factor 4 (HPF4) antibodies.

We describe 3 patients in whom bullous hemorrhagic dermatosis developed without thrombosis of dermal vessels at sites distant from subcutaneous injections of heparin. The mechanism of blister formation remains unexplained.

CASE REPORTS

Case 1

A 75-year-old man with a history of ischemic heart disease and hypothyroidism was hospitalized for unstable angina. His medications included furosemide, diltiazem, amiodarone, simvastatin, transdermal glyceryl trinitrate, thyroxin, and aspirin. LMWH (dalteparin, 100 anti-Xa U/kg twice daily by subcutaneous injections) was the only new drug introduced on admission. Five days later approximately 50 bullae developed in his groin (Fig 1, A) and on the backs of his hands. Physical examination revealed tense hemorrhagic bullae on otherwise normal skin. Mucous membranes were normal and there was no pruritus. A biopsy specimen of the bullae was obtained and showed intraperiostal bullae filled with red blood cells, normal blood vessels, and a moderate perivascular lymphohistiocytic infiltrate (Fig 1, B). Direct immunofluorescence test showed no complement or antibody deposition. Activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen levels, fibrin degradation products, D dimers, and ethanol gelation test results were normal. Blood cell count including platelet count, urea and electrolyte levels, and liver function tests were also normal. Urinary porphyrin levels were normal. Anti-intercellular cement substance and anti–basement membrane zone antibodies were not detected on indirect immunofluorescence studies.

Plasma anti-Xa levels were 0.43 U/mL and 0.72 U/mL 24 hours and 7 days after initiation of heparin, respectively. Coronary angiography 2 days after onset of the dermatosis showed severe lesions that required coronary stenting. Oral anticoagulants were initiated 7 days after onset of the bullous dermatosis.

Abbreviations used:

- APTT: activated partial thromboplastin time
- DLF: direct immunofluorescence
- HPF4: heparin-platelet factor 4
- LMWH: low-molecular-weight heparin
- PT: prothrombin time
- UFH: unfractionated heparin

![Image 1](image1.png)

**Fig 1.** Patient 1. A, Tense hemorrhagic blisters located on arm. B, Histologic examination shows well-limited intraperiostal bullae filled with red blood cells. Note absence of microthrombi within dermal vessels. (Hematoxylin, eosin, and safranin stain; original magnification: ×100.)

![Image 2](image2.png)

**Fig 2.** Patient 2. A, Hemorrhagic blisters located on leg. B, Histologic examination shows intra-epidermal bullae filled with red blood cells. C, Higher magnification. (B and C, Hematoxylin, eosin, and safranin stain; original magnifications: B, ×40; C, ×200.)
Letters to the Editor

A rare cutaneous manifestation of hemorrhagic bullae to low-molecular-weight heparin and fondaparinux: report of two cases

Keywords: bullae, cutaneous, dermatosis, hemorrhagic bullae, heparin

To the Editor:

Heparin, unfractionated (UFH) or low-molecular-weight (LMWH), is a parenteral anticoagulant, which exerts its anticoagulant effect by activating antithrombin III (AT) activity. Heparin-induced cutaneous reactions occur with a reported incidence of 7.5%, are commonly localized to the injection site, and include contact dermatitis, ecchymotic plaques, arcana lesions, ecchymoses, hematoma, calcification, rash, urticaria, and skin necrosis. Skin necrosis is also seen in heparin-induced thrombocytopenia (HIT), in which antibodies to heparin-dependent factor 4 (HDPF4) induce dermal vessel thrombosis. HIT mimics with systemic symptoms such as fever, chills, dyspnea, and pleuritic chest pain. The same antibodies are accompanied by thrombocytopenia. Heparin-induced hemorrhagic bullae at a location distant from the injection site are rare, and have only been reported 26 times in the literature to include the two cases described below.

Patient 1

In January 2012 at the Hematology Clinic of Duke University, a 51-year-old woman was placed on heparin after closure of the central retinal artery. She was eventually switched to enoxaparin, a LMWH, and aspirin as an outpatient. In September 2012, she complained of “dark spots” on her calf which gradually enlarged to bullae (Fig. 1A).

Patient 2

At the same clinic, a 51-year-old Hispanic woman was started on enoxaparin for recurrent pulmonary emboli. She was later switched to fondaparinux, a second-generation LMWH. In February 2013, 3 months after patients 1 was started, the patient also presented. Patient 2 complained of “blood blisters” on her lower extremities (Fig. 1B).

Physical examination of both patients demonstrated hemorrhagic bullae on the postero-lateral lower extremities. The bullae were tense but were otherwise located on a normal appearing skin. Aside from these findings, no other findings were noted. Pericarditis or other signs of bleeding were not identified.

Laboratory studies including a complete blood count, platelet count, and FDP antibodies of both patients were negative. The differential diagnosis ruled out heparin or warfarin-induced necrosis, antiphospholipid syndrome, bullous disease with hemorrhage, and necrotizing cutaneous vasculitis, epidermolysis bullosa acquisita, bullous lichen planus, Sweet’s syndrome, angiod streaks, and nicotine-induced bullae. The combined clinical presentation and laboratory data of both patients excluded the possibility of HIT.

Histopathologic examination of hematoxylin–eosin stained sections of the first patient’s lesions demonstrated red blood cell extravasation in the dermis and intradermal blister-like serum deposition. An endothelial lining to indicate intradermal red blood cells are present.

Fig. 2. Skin biopsy from the lower extremity of Patient 1 with hematoxylin-eosin stain demonstrating extravasated red blood cells in the dermis and bullae formation in the epidermis. No eosinophils, vasculitis, or thromboemboli are seen (x100).
Further history and investigations

• Skin changes for one week (starting on the back and rapidly spreading on trunk, upper extremities, face)
• 3 week before mild pharingytis
• Worsening with local steroid treatment
• No other relevant symptoms
Exanthemathatic psoriasis

- Abrupt onset, often after an infection (in children commonly streptococcal pharyngitis)
- Lacks the typical clinical features of chronic plaque-type psoriasis; not always pustular
- May resolve or progress into conventional psoriasis
Lysozyme  MPO
3 months earlier
Further history and investigations

• Atopic dermatitis since October 2011
• Alternation of improvement and worsening for 4 years
• Lack of response to conventional treatment; 4 skin biopsies over 36 months (consistent with atopic dermatitis)
• July 2014: pancytopenia; bone marrow biopsy shows myelodysplastic syndrome
• October 2015: bone marrow biopsy shows progression to AML
• October 2015: skin biopsy shows specific cutaneous manifestations of AML on the background of atopic dermatitis
• Exitus September 28, 2016
In contrast to B-CLL, skin infiltrates of myelogeneous leukemia are seen only rarely at the site of skin inflammation.

Sweet syndrome-like infiltrates represent probably a mimicker rather than a true colonization of Sweet syndrome by AML cells, but exceptions exist and the relationship between the two disorders has not been fully elucidated yet.
LETTER TO THE EDITOR

Leukemia cutis limited to the needle puncture sites

Dear Editor,

Leukemia cutis is a rare dermatological manifestation of leukemia, typically involving skin lesions that appear at the site of needle punctures. The exact incidence of this condition is unknown, but it is estimated to occur in less than 1% of patients with leukemia. The development of leukemia cutis is usually associated with hematological malignancies, particularly acute myeloid leukemia (AML) and chronic myeloid leukemia (CML).

In our recent case study, we observed a patient with CML who presented with multiple skin lesions at the sites of needle punctures, which were confirmed to be leukemia cutis. The patient had a history of CML for several years, and the skin lesions appeared after repeated blood draws and intravenous (IV) infusions. The lesions were characterized by erythematous, indurated plaques with a purpuric component, and histological examination revealed aggregates of leukemic blasts in the dermis.

We believe that the occurrence of leukemia cutis at needle puncture sites is a result of the trauma caused by repeated injections, leading to an increased risk of leukemic cell dissemination. Therefore, it is crucial to be vigilant in monitoring patients with hematological malignancies who undergo frequent blood draws or IV therapies. Early recognition and diagnosis of leukemia cutis are important to prevent complications and improve patient outcomes.

In conclusion, we recommend that clinicians be aware of the potential for leukemia cutis to occur at needle puncture sites in patients with hematological malignancies. Further research is needed to better understand the underlying mechanisms and to develop effective management strategies.

Yours sincerely,

[Author Name]

[Hospital/Institution]
Leukemic cells within skin lesions of psoriasis in a patient with acute myelogenous leukemia

We report on an 81-year-old man with acute myelomonocytic leukemia (FAB M4) and a long-standing history of psoriasis. Biopsies of psoriatic plaques revealed the coexistence of characteristic histopathologic aspects of psoriasis together with an infiltrate of blasts with features of myelomonocytes, suggestive of a specific leukemic infiltrate within plaques of psoriasis. Immunohistochemical stainings showed positivity of blasts for LN2 (CD74), MT1 (CD43), and lysozyme, consistent with a myeloid lineage of these cells. To the best of our knowledge, this is the first report on the association of psoriasis with myelogenous leukemia. The presence of leukemic cells within psoriatic skin plaques may be explained by non-specific recruitment of recirculating malignant cells to the skin. Alternatively, as psoriasis is an inflammatory disease involving granulocytes among other cell types, it may be hypothesized that leukemic cells retain to some extent their capability to respond to physiologic stimuli and enter the skin in response to specific chemotactic factors.


Specific skin involvement can be observed in more than 10% of patients with acute myelogenous leukemia (AML) (1). Clinical manifestations are usually characterized by generalized erythematous papules, plaques or nodules. Skin infiltrates may precede, be concomitant with or arise after leukemic blood involvement. We describe a patient with acute myelomonocytic leukemia presenting with infiltrates of leukemic cells within skin lesions of psoriasis.

Case report

An 81-year-old man with a long-standing history of psoriasis localized to the elbows presented with increasing fatigue, anemia and leukopenia. Bone marrow examination showed diffuse infiltration of myelomonocytic blast cells positive for CD15, CD14, CD15 and CD53. According to these findings, a diagnosis of AML (FAB-M4) was made. Due to the advanced age and no chemotherapy was administered, and the patient was followed up at short intervals.

At the same time, the patient experienced a sudden generalization of psoriasis with manifestations on previously uninvolved skin such as the trunk and both lower extremities (Fig. 1). In order to rule out uncommon skin infiltrates of myelomonocytic leukemia, three 4-mm punch biopsies were obtained from lesions on both lower legs. Specimens were fixed in 4% buffered formalin and embedded in paraffin for routine histopathologic and immunohistochemical studies.

Histopathology. All three skin biopsies revealed similar histopathologic features. The epidermis showed a marked psoriasiform acanthosis (Fig. 2). Neutrophils could be observed within both the epidermis and a parakeratotic horny layer. Demal papillae were elongated and characterized by the presence of dilated, tortuous blood vessels (Fig. 2). In the upper dermis there was a relatively dense infiltrate composed of lymphocytes and histiocytes mingled with numerous medium-sized and large atypical mononuclear cells (Fig. 3). Cytoplasm of atypical cells was characterized by irregular nuclei with prominent nucleoli and
F, 24, pregnant (22nd week)
Further history and investigations

- 22th week of pregnancy
- 14 days before was bitten by a cat; the wound was managed surgically; *Pasteurella multocida* identified by a smear
- Treatment with unasyn (ampicillin and sulbactam); 10 days after beginning of antibiotic treatment onset of exanthema
- DIF and IIF negative; almost complete resolution within 2 weeks after discontinuation of the antibiotic treatment
Drug eruption in pregnancy
Pregnancy dermatoses

- Pemphigoid gestationis: any trimester or immediately post-partum (classically in late pregnancy)
- PEP (PUPP): last part of 3rd trimester or immediately post-partum
- Intraepathic cholestasis of pregnancy: 3rd trimester
- Atopic eruption of pregnancy: mostly during the 1st trimester
- Eosinophils may be seen in many pregnancy dermatoses; histopathological features oft mimic those of hypersensitivity reactions
Not every dermatosis during pregnancy is a pregnancy dermatosis

Arthropod bite reaction in pregnancy
Further history and investigations

- Histopathological diagnosis of melanoma in situ.
- Patient sent to urological investigation prior to conservative complete excision.
- A large mass is found surrounding the urethra in the distal portion of the penis.
Melanoma extending from the urethra

- Melanoma can rarely arise within the urethra (and the prostate, and the urinary bladder)
- Sometimes symptoms are subtle (or ignored by the patients)
- In situ extension along the urethra can lead to involvement of the genital skin / mucosa, where the first diagnosis may be made
- Urological examination of "primary" genital melanoma (even in situ !) mandatory
Primary malignant melanoma of the urethra: a systematic analysis of the current literature

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Abstract

Background: Primary malignant melanoma of the urethra is a rare tumour that more commonly affects the mucous and distal urethra. General prognosis seems to be poor. To date, there have been no systematic reviews on this topic. Therefore, we aimed to gain more insight into this rare type of cancer.

Methods: Medline and PubMed were searched, and all cases of urethral melanoma reported or single case reports or small case series were reviewed as the first step in the combined analyses of all the cases reported.

Results: We reviewed 150 cases. The most frequent presentation was urethral mass. The first line of treatment was surgery such as a partial or total uretrectomy. Three out of four women were diagnosed with an average age of 64.7 years (SD 10.2; median 55; range 28–96 years). Forty-three patients (29%) underwent adjuvant treatment, including chemotherapy, radiotherapy, or immunotherapy. Recurrences were observed in 71.4% (n = 80) of the cases, mainly local recurrences (n = 44; 55%) and metastases in the inguinal lymph nodes (n = 31; 28%). Recurrences occurred within 12.5 months on average (SD 12.6; range 1–48).

Conclusion: Urethral melanoma is a rare disease of older people with an average age of 64 years. The study showed that the 7-stage as a basis of depth invasion is a prognostic factor for urethral melanoma. Moreover, p16 expression, presence of p16 expression, and systemic recurrence influence prognosis. The 7-stage classification is useful because of its prognostic ability.

Keywords: Female urethra – Malignant melanoma – Long-term survival

Introduction

Primary malignant melanoma of the urethra is mainly located in the skin and the eyes. Those of the genital tract represent less than 1% of all melanomas. In embryology, the urethra develops from endodermal origin but melanocytes originate primarily from neural crest tissue. This is the reason for the low incidence of melanoma in the urethra [11]. After the first case report of this melanoma by Read [12],
Further history and investigations

- *Borrelia* serology: IgG+, IgM+
- *Borrelia* PCR on biopsy: positive
Interstitial granulomatous dermatitis

- A histopathologic reaction pattern, observed mostly in patients with rheumatoid arthritis or autoimmune collagen diseases
- May be observed in drug eruptions and rarely in infection by *Borrelia*
- Histiocytic "pseudorosettes" are characterized by fragments of collagen fibers surrounded by histiocytes
Interstitial granulomatous dermatitis with hystiocytic pseudorosettes: A new histopathologic pattern in cutaneous borrelialosis. Detection of *Borrelia burgdorferi* DNA sequences by a highly sensitive PCR-ELISA

Carmen Moreno, MD,1 Helena Ramonc, MD,1 Gabriele Enrico, MD,1 Elise Gorrelit, MD,2 Loretta Cappea, MD1 and Luis Requena, MD2

**Background:** The cutaneous manifestations of Borrelia burgdorferi infection include an early phase of erythema migrans and a late phase of annular dermal atrophic nodules.

**Objective:** To describe a pattern with peculiar cutaneous involvement and intense histopathologic findings in cutaneous borrelialosis.

**Methods:** Eleven patients with a presumptive clinical diagnosis of cutaneous borrelialosis showed typical histopathologic findings on skin biopsies. Immunohistochemical analysis was used to detect *Borrelia burgdorferi* DNA sequences in all patients. Immunohistochemical findings were also studied by light microscopy.

**Results:** Nine patients presented the characteristic appearance of cutaneous borrelialosis, whereas the other two patients showed different histopathologic findings. Immunohistochemical analysis demonstrated *Borrelia burgdorferi* DNA sequences in all cases, except in one patient with clinical neuroborrelialosis and histopathologic findings compatible with a pseudorosette reaction. In one case, the DNA sequences were detected in a dense perivascular infiltrate.

**Conclusion:** Cutaneous lesions in patients with clinical and laboratory evidence of ricketsial and *Tularemia* infections may resemble those of cutaneous borrelialosis. Immunohistochemical analysis of skin biopsies can be used to detect early phases of cutaneous borrelialosis.

In 1982, Ribbert et al. included a new infection, now called *Borrelia burgdorferi* as the etiologic agent of Lyme disease. Shortly thereafter, it was demonstrated that ticks were vectors of the disease and responsible for vector-borne transmission. Today, Lyme disease is the most commonly reported vector-borne disease in the United States, and it is estimated that over 100,000 new cases are diagnosed annually. The disease is characterized by a triphasic clinical course, with the early acute phase characterized by erythema migrans, the subacute phase by disseminated skin lesions, and the chronic phase by intermittent skin and disseminated systemic involvement. Lyme disease is caused by *Borrelia burgdorferi*, a bacterium that is transmitted to humans through the bite of an *Ixodes* tick. The disease can be effectively treated with antibiotics, and early diagnosis is crucial for optimal treatment outcomes.

Erythema migrans is the initial manifestation of Lyme disease and is characterized by a characteristic, annular rash that appears at the site of the tick bite and spreads centrifugally. The rash is typically red, with a clear central area and well-defined borders. If left untreated, Lyme disease can progress to disseminated chronic skin and systemic manifestations, including arthritis, neurologic symptoms, and carditis. Early diagnosis and treatment with antibiotics, often a combination of doxycycline and amoxicillin, can prevent the development of chronic manifestations.

Lyme disease is diagnosed through a combination of clinical features and laboratory testing. The diagnosis is often confirmed by the presence of specific antibodies against *Borrelia burgdorferi* in serum or cerebrospinal fluid. Serologic testing can be performed using enzyme-linked immunosorbent assay (ELISA) and Western blotting. The ELISA test is usually the first test performed, and a positive result should be confirmed with a Western blot to identify the specific antibodies. In some cases, PCR testing may also be used to detect *Borrelia burgdorferi* DNA in blood or other body fluids.

The management of Lyme disease is based on the stage of the disease and the presence of co-morbidities. The early acute phase of the disease is typically treated with antibiotics, and the duration of treatment is based on the clinical presentation and the patient's response to therapy. In more chronic cases, treatment may be extended to suppress the infection, and corticosteroids may be used to manage symptoms of arthritis or meningitis. Early diagnosis and treatment are essential to prevent the development of chronic manifestations and reduce the risk of long-term sequelae.
Further history and investigations

• After histopathological diagnosis on skin biopsy a rheumatoid arthritis was discovered
Railway track dermatitis

- Reported in 1965 by Dickman et al. as "linear subcutaneous bands in rheumatoid arthritis", subsequently as "interstitial granulomatous dermatitis with cutaneous cords and arthritis", "rope sign", "linear granuloma annulare", "linear rheumatoid nodule", "interstitial granulomatous dermatitis with plaques", and "railway track dermatitis"

- Associated with rheumatoid arthritis, rarely with other autoimmune disorders including SLE
Linear Subcutaneous Bands in Rheumatoid Arthritis
An Unusual Form of Rheumatoid Granuloma

Calvin J. Dykman, M.D., Gilbert J. Gales, M.D., and Armin E. Good, M.D.
Ann Arbor, Michigan

Subcutaneous nodules are rather common extra-articular manifestations of rheumatoid arthritis, characteristically appearing as rounded, firm tender structures overlying pressure areas. This report concerns two patients with classical rheumatoid arthritis, Seger III, Class III, who in addition to numerous subcutaneous nodules had striking subcutaneous linear bands that were histologically compatible with rheumatoid granuloma. Elongated subcutaneous lesions are unique in our experience and have not to our knowledge, been previously described as a manifestation of rheumatoid arthritis.

Case Reports

Case 1

Patient: J. R. (Ann Arbor V. A. No. 014401), a 39-year-old white male, was admitted to the Ann
INTERSTITIAL GRANULOMATOUS DERMATITIS WITH CUTANEOUS CORDS AND ARTHRITIS:
LINEAR SUBCUTANEOUS BANDS IN RHEUMATOID ARTHRITIS REVISITED

Geoffrey J. Gottlieb, MD, Ralf Stefan Duve, MD,
A. Bernard Ackerman, MD

In 1965, Dykman et al. reported on their experience with two patients who had what they called "linear subcutaneous bands in rheumatoid arthritis: an unusual form of rheumatoid granuloma." The crucial clinical features were painless, skin-colored, firm cords situated mostly on the lateral aspect of the trunk, one pole of these cords extending to the axilla (Fig. 1). Histopathologic examination of sections from a specimen taken from a cord revealed "extensive degeneration of collagen fibers with an infiltrate of lymphocytes, histiocytes, and fibroblasts." The authors considered the findings to "resemble those seen in rheumatoid nodules." Both patients had clinical and serologic evidence of rheumatoid arthritis.

In 1964, at the annual meeting of the American Society of Dermatopathology, one of us (CJG) presented two patients with skin lesions very similar to those of the patients of Dykman et al. The findings by conventional microscopy, however, were not those of rheumatoid nodules, but of a distinctive interstitial and palisaded granulomatous dermatitis. Although both patients had a symmetrical arthritis consistent with rheumatoid arthritis, neither demonstrated serologic evidence of rheumatoid factor.

Because so little has been written since then about this intriguing subject, except for a single case report by Harms et al., that chronicled a case of what they called "linear granuloma" and because we have now studied at least ten other examples of it, we set down here the characteristic histopathologic attributes of the condition.
Interstitial granulomatous dermatitis with plaques

Carlo Tommasi, MD, and Mario Pimpine, MD Turin, Italy

Background: Interstitial granulomatous dermatitis is a dermatologic entity with variable clinical presentation associated with autoimmune systemic diseases. The frequency of different autoimmune and interstitial diseases in this entity is not known.

Objective: To describe the clinical behavior and biological features of 17 patients with interstitial granulomatous dermatitis in a clinical presentation consisting of large, plaquelike lesions.

Method: A retrospective study of 17 patients with interstitial granulomatous dermatitis was performed. Clinical and laboratory data were reviewed.

Results: The study included 10 men and 7 women with a mean age of 52 ± 11 years. In all cases, large plaques were present. Histologically, the lesions showed a rich infiltrate of lymphocytes, histiocytes, and plasma cells, with granulomas in some cases. The disease was associated with autoimmune systemic conditions in 11 patients (65%). The most common associated diseases were rheumatoid arthritis, systemic lupus erythematosus, and mixed connective tissue disease.

Conclusions: Interstitial granulomatous dermatitis with plaques is a distinctive clinicopathologic entity, frequently associated with autoimmune systemic conditions. Further study is needed to better understand its pathogenesis and clinical behavior.

Table 1. Summary of clinical features of 17 patients with IGD with plaques

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Site</th>
<th>Extramembranous disease</th>
<th>Serosal lesions</th>
<th>Drug</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>56</td>
<td>Lateral chest wall, thighs</td>
<td>Rheumatoid arthritis</td>
<td>Anti-thyroid Ab</td>
<td>NED</td>
<td>12 mo</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>70</td>
<td>Lateral chest wall, inguinal, abdominal, thighs</td>
<td>Rheumatoid arthritis</td>
<td>Anti-thyroid Ab</td>
<td>NED</td>
<td>20 mo</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>49</td>
<td>Abdomen, legs</td>
<td>Thyroiditis, allergic asthma</td>
<td>Anti-thyroid Ab</td>
<td>PD</td>
<td>36 mo</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>68</td>
<td>Abdomen, lateral chest wall</td>
<td>Rheumatoid arthritis</td>
<td>Anti-aggregation agents</td>
<td>Alpha-blocking</td>
<td>NED</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>52</td>
<td>Lateral chest wall, abdomen, thighs</td>
<td>Villitis, rheumatoid arthritis</td>
<td>Anti-thyroid Ab</td>
<td>PD</td>
<td>32 mo</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>52</td>
<td>Lateral chest wall, upper extremities</td>
<td>Rheumatoid arthritis</td>
<td>Anti-thyroid Ab</td>
<td>PD</td>
<td>22 mo</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>54</td>
<td>Lateral chest wall, upper extremities</td>
<td>Rheumatoid arthritis</td>
<td>Anti-thyroid Ab</td>
<td>NED</td>
<td>16 mo</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>29</td>
<td>Lateral chest wall, legs</td>
<td>Rheumatoid arthritis</td>
<td>Anti-thyroid Ab</td>
<td>PD</td>
<td>22 mo</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>22</td>
<td>Lateral chest wall, inguinal, abdominal, thighs</td>
<td>Rheumatoid arthritis</td>
<td>Anti-thyroid Ab</td>
<td>NED</td>
<td>16 mo</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>62</td>
<td>Lateral chest wall</td>
<td>Rheumatoid arthritis</td>
<td>Anti-thyroid Ab</td>
<td>NED</td>
<td>13 mo</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>60</td>
<td>Thighs</td>
<td>Rheumatoid arthritis</td>
<td>Calcium channel blockers, ACE inhibitors, thiazides</td>
<td>PD</td>
<td>18 mo</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>44</td>
<td>Inguinal, thighs</td>
<td>Rheumatoid arthritis</td>
<td>Calcium channel blockers, ACE inhibitors, thiazides</td>
<td>PD</td>
<td>24 mo</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>26</td>
<td>Thighs</td>
<td>Rheumatoid arthritis</td>
<td>Anti-thyroid factor</td>
<td>PD</td>
<td>8 mo</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>74</td>
<td>Thighs, upper extremities</td>
<td>Rheumatoid arthritis</td>
<td>Anti-thyroid factor</td>
<td>NED</td>
<td>18 mo</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>60</td>
<td>Lateral chest wall</td>
<td>Systemic lupus erythematosus</td>
<td>Anti-thyroid factor, anti-TNF-α</td>
<td>PD</td>
<td>3 mo</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>43</td>
<td>Thighs</td>
<td>Rheumatoid arthritis</td>
<td>Anti-thyroid factor, anti-TNF-α</td>
<td>PD</td>
<td>3 mo</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>62</td>
<td>Lateral chest wall, inguinal, thighs</td>
<td>Rheumatoid arthritis</td>
<td>Anti-thyroid factor, anti-TNF-α</td>
<td>PD</td>
<td>3 mo</td>
</tr>
</tbody>
</table>

All: Antibodies; ANA, anti-nuclear antibodies; NED, no evidence of disease; PD, persistence of disease.

*After appearance of disease.
"pseudorosettes"
M, 35, with history of chronic GVHD
Further history and investigations

- Testicular carcinoma 2011; semi-castration, chemotherapy
- Therapy-associated AML 7/2014
- Allogenic stem cell transplantation 10/2014
- Acute GvHD 2/2015
- CMV-reactivation, EBV-reactivation
- Plasmapheresis
- Recurrent GvHD 4/2016 (skin grade 1, gastrointestinal grade 4)
- Extracorporeal photopheresis
- Progressive induration of the skin
M, 35, with history of chronic GVHD

**Graft versus Host Disease**

*sclerodermatous, nodular*
Sclerodermiform GvHD

- A clinicopathological variant of chronic cutaneous GvHD with clinicopathological similarities to morphea / scleroderma
- A nodular ("keloidal") form of morphea well known; a similar variant of sclerodermiform GvHD not well described
- Clinically nodular and plaque-like indurations; histopathologically scar-like tissue mainly in the superficial part of the dermis (akin to keloidal morphea)
Nodular Morphea

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Key Words
Scleroderma • Keloid • Hypertrophic scar • Morphea

Abstract
Scleroderma may present as being strictly limited to the skin, as in morphea, or within a multiglandular disease, as in systemic sclerosis. Accordingly, cutaneous manifestations vary clinically. In nodular or keloidal scleroderma, patients develop lesions that are clinically indistinguishable from a keloid; however, the histopathological findings are more variable. We describe a 16-year-old girl with morphea lesions for 4-5 years and additional development of keloidal nodules within these lesions. The histological examination revealed a hypertrophic scar besides morphea.

Introduction
Several clinical presentations of both systemic and localized scleroderma are described. The nodular or keloidal variant is one of the rarest forms. It was first described by the English physician Thomas Addison in the mid 1800s as “true keloid.” Later on, Paul Gerson Unna included an article about this variant of scleroderma in his textbook on the histology of skin disease [1-3].

Nodular scleroderma can occur in association with progressive systemic sclerosis or with localized morphea. It mostly affects young and middle-aged women. The firm elevated nodules, which can range in size from 2 mm to 4-5 cm, usually appear spontaneously and tend to involve the trunk and upper extremities. A linear presentation has also been described. The literature on this topic is confusing because the term “nodular scleroderma” and “keloidal scleroderma” are used interchangeably even though there is a great degree of variability in the histological findings of these nodules [4]. In contrast, other authors stress that the cutaneous manifestations may vary clinically, but all share the same histopathological pattern of both morphea/scleroderma and keloid [5].

Nodular or keloidal scleroderma may represent a keloidal response of the inflamed skin that is already involved in an active fibrotic process inherent to the disease in those patients who are genetically predisposed to keloid development, or at sites of the skin that show a high predisposition for keloid formation, such as the trunk [6, 7].

Case Report
Medical History
A 16-year-old girl presented with multiple progressive morphea skin lesions limited to the abdomen. These lesions had developed over the course of 3-4 years without any tendency to heal. Six months

Fig. 1. Clinical presentation of the morphea and nodular lesions. The biopsy was taken from the keloidal margin of the right upper paraumbilical lesion.

Fig. 2. Morphea plaque with nodular erythematous lesions on the border.

Fig. 3. This acellular, bordered erythematous nodule with its slightly “forme fruste” is reminiscent of the clinical variant of superficial scleroderma Panniculitis.

Fig. 4. Low magnification of the histological findings from a biopsy of a nodule: a slightly elevated hypertrophic scar with an increased number of fibroblasts and collagen bundles. Scale bar = 200,000 μm.

Fig. 5. Higher magnification of the hypertrophic scar tissue: parallel collagen bundles with numerous fibroblasts and perpendicular oriented capillaries with a sparse inflammatory infiltrate. Scale bar = 500 μm.
Nodular Scleroderma: A Report of 2 Cases

Cooper C. Wriston, BA, Adam I. Rubin, MD, Rosalie Elenitsas, MD, and Glen H. Crawford, MD

Abstract: Nodular scleroderma, also known as keloidal scleroderma, is a rare form of scleroderma that may occur with either systemic sclerosis or localized scleroderma. Clinically, this disorder is characterized by keloidal nodules that form in sclerodermatous areas. These nodules may histologically show the presence of keloidal collagen. Because of the rarity of this condition, clinicians may not be familiar with the clinical and histologic features relevant to this scleroderma variant. In this report, we describe 2 cases of nodular scleroderma.

Key Words: nodular scleroderma, keloidal scleroderma, nodular morphea

Am J Dermatopathol 2008;30:385-388

The cases presented here were encountered in the University of Pennsylvania Health System. Biopsy specimens were formalin-fixed, paraffin-embedded, and sections were stained with hematoxylin and eosin using routine procedures.

CASE REPORTS

Case 1

A 35-year-old man with a medical history of systemic sclerosis (scleroderma) presented for the evaluation and management of multiple hyperpigmented nodules. Nine years earlier he had been diagnosed with systemic sclerosis after developing polyarthalgia, Raynaud phenomenon, and symptoms of nephropathy. One year after his diagnosis, he developed multiple nodules and plaques on his mid-chest and intracarpal back. There was no history of trauma or surgery in any of the involved areas. The physical examination revealed polycyclic, firm nodules and plaques on his mid-chest and intracarpal back (Fig. 3). Hypertrophied tissue was noted in areas of sclerodermatous change. A 4-mm punch biopsy of a nodule on the intracarpal back revealed dermal fibrosis with thickened keloidal collagen bundles (Fig. 2). Hypertrophied collagen bundles were present, and dermal fibrosis was noted in areas of sclerodermatous change. A 4-mm punch biopsy of a nodule on the intracarpal back revealed dermal fibrosis with thickened keloidal collagen bundles (Fig. 2). Hypertrophied collagen bundles were present, and dermal fibrosis was noted in areas of sclerodermatous change. A conspicuous inflammatory infiltrate was not present. The histologic specimen showed features of both scleroderma and keloid when compared to normal skin and other affected areas. These biopsy findings were correlated with the clinical history and examination findings, the diagnosis of nodular scleroderma (NS) was made.

The patient elected to treat several nodules with intralesional triamcinolone (10 mg/mL) every 6 weeks. After 4 months of triamcinolone injections, the lesions had not changed.

Case 2

A 30-year-old woman presented for evaluation of multiple hyperpigmented papules and plaques on the chest, proximal arms, and thighs of 2 years' duration. She had previously been diagnosed with mixed connective tissue disease by a local rheumatologist. Her history was significant for pericarditis, distal digital ulceration, sclerodermy, Raynaud phenomenon, and polyarthralgia. After her diagnosis, pruritic papules and plaques developed on her chest. These lesions were treated with topical corticosteroids by a local dermatologist with good improvement. Serologic testing performed 1 month before her initial visit in our clinic revealed positive anti-nuclear (ANA, 1:2500) and anti-nuclear ribonucleoprotein (RNP) antibodies. Rheumatoid factor, Ro, La, double-stranded DNA, and Smith were negative.

The physical examination revealed sclerodermy and several punctate digital scars. Multiple indurated, hyperpigmented papules and plaques were present across the chest and the proximal upper and lower extremities (Fig. 3). After the diagnosis of scleroderma was made, a 4-mm punch biopsy of a papule on the left chest was performed. It revealed scar formation and keloidal collagen (Fig. 4). A conspicuous inflammatory infiltrate was not present. Clinico-pathologic correlation of the biopsy findings with the cutaneous examination resulted in a diagnosis of NS.

The patient began intralesional triamcinolone (10 mg/mL) for the lesions on her chest. Injections were performed at 6-week intervals and resulted in a modest improvement in the clinical appearance after 6 months of therapy.

DISCUSSION

NS is a rare type of scleroderma that is characterized by multiple, firm, keloidal nodules or plaques. These nodules have been reported in linear, local, and general distributions on the chest, back, neck, and proximal extremities (Table 1). The lesions can be asymptomatic or pruritic. NS has been reported in the context of both localized and systemic scleroderma. Although the terms NS and keloidal scleroderma are often used interchangeably, some authors have made histologic or clinical distinctions between the two. For example, Barzilai et al. suggested that the term "keloidal scleroderma" be reserved for cases that are both clinically and histologically similar to keloid while the term "nodular scleroderma" be used for cases that are histologically similar to scleroderma. NS occurs more frequently in females in their third, fourth, or fifth decade of life. In many circumstances, symptoms of scleroderma precede the disease.
Review of Cutaneous Graft-vs-Host Disease

R. Ballester-Sánchez, M. Navarro-Mira, J. Sanz-Caballer, R. Botella-Estrada

Servicio de Dermatología, Hospital Universitario yPolitécnico La Fe de Valencia, Valencia, Spain
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Abstract: Graft-versus-host disease (GVHD) is a multisystem disease that arises as a complication of allogeneic hematopoietic stem cell transplant. It is due to recognition of the recipient's tissues by immune cells from the donor. The skin and mucosal membranes are the organs most commonly affected. GVHD is classified as acute or chronic depending on the pathophysiology and clinical presentation. Acute GVHD typically presents with the triad of rash, diarrhea, and hyperferritinemia. Treatment is based on systemic corticosteroid and immunosuppressive therapy. The cutaneous manifestations of chronic GVHD are divided into sclerodermiform and mucocutaneous forms, and the mucous membranes and skin appendages may also be affected. The diagnosis is largely clinical, but skin biopsy can help in classification. Treatment can be topical, systemic, or physical, depending on the site, type, and severity of the lesions and the involvement of other organs.

PALABRAS CLAVE: Enfermedad inmunológica contra huésped cutáneo; Dermatología

Aproximación a la enfermedad inmunológica contra huésped cutáneo

Resumen: La enfermedad inmunológica contra huésped (EICH) es una enfermedad multissistemática que se presenta como complicación de un trasplante de progenitores hematopoyéticos alógunos. Se basa en el reconocimiento de los tejidos del receptor por parte de los linfocitos inmunocompetentes del donante. La piel y las mucosas son los órganos más frecuentemente afectados. Se clasifica en forma aguda o crónica, en función de la fisiopatología y presentación clínica. La presentación se basa en el triada de rash, diarrea y elevación de la ferritina. El tratamiento se basa en el uso de corticoides e inmunosupresores sistémicos. Las manifestaciones cutáneas de la enfermedad inmunológica contra huésped son variables y se manifiestan en diferentes formas. Pueden afectar también mucosas y órganos internos. El diagnóstico se efectúa clínicamente, pero la biopsia cutánea puede ayudar a confirmarlo. El tratamiento puede ser tópico, sistémico o mixto, en función de la extensión, localización y severidad de las lesiones y afectación de otros órganos.

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M, 80
Polyclonal gammopathy and previously treated Borrelia infection.
Further history and investigations

- April 2014: 7 kg. weight loss, anemia, multiple erythematous macules on trunk and extremities; *Borrelia* serology IgM+, IgG+; diagnosis of "lymphadenosis cutis dispersa"
- Antibiotic treatment for 3 weeks (ceftriaxone)
- July 2014: persistent skin lesions; *Borrelia* serology IgM+, IgG+ (higher titer than in April); polyclonal gammopathy
- December 2014: persistent skin lesions; polyclonal gammopathy persists
- September 2016: comes back with persistent skin lesions; persistent polyclonal gammopathy
- *Borrelia*-PCR positive on biopsy specimen
Persistent Borreliosis with polyclonal gammopathy
Persistent *Borreliosis*

- Some patients present persistent symptoms after antibiotic treatment of *Borrelia* infection ("post-Lyme disease syndrome")
- It is unclear whether all or only some of these patients have a genuine persistent infection
- Prolongued antibiotic treatment does not influence the outcome
Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease

Anneleen Benyamin, M.D., Hadavchi M.J., van Hooft, M.D., Ph.D., Fidel J. Vos, M.D., Ph.D., Hendrik van Milicen, M.D., Ph.D., Michel H. Vossenaar, M.Sc., Mitja Trepca, Ph.D., Frank H. van der Vinck, M.D., Ph.D., A. Roijer T. Donders, Ph.D., Andrea M. Evers, Ph.D., and Bart van Kuijk, M.D., Ph.D.

ABSTRACT

BACKGROUND

The treatment of persistent symptoms attributed to Lyme disease remains controversial. We assessed whether longer-term antibiotic treatment of persistent symptoms attributed to Lyme disease leads to better outcomes than shorter-term treatment.

METHODS

In a randomized, double-blind, placebo-controlled trial conducted in Europe, we assigned patients with persistent symptoms attributed to Lyme disease—either relapsing or nonrelapsing—to receive a 12-week oral course of doxycycline, clarithromycin plus tinidazole, or placebo. All study groups received open-label intranasal corticosteroids for 2 weeks before initiating the randomized regimen. The primary outcome measure was health-related quality of life, as assessed by the physical component summary score of the SF-36 Health Status Questionnaire (1920 to 1940 points, 0 to 100, with higher scores indicating better quality of life) at the end of the treatment period, or week 34. After the 2-week course of corticosteroids and the 12-week course of the randomized study drug or placebo had been completed.

RESULTS

Of the 391 patients who underwent randomization, 90 were included in the modified intention-to-treat analysis (80 patients in the doxycycline group, 90 in the clarithromycin-hydroxychloroquine group, and 90 in the placebo group). The SF-36 physical component summary scores did not differ significantly among the three study groups at the end of the treatment period, with mean scores of 49.0 (95% confidence interval [CI], 43.1 to 54.9) in the doxycycline group, 45.6 (95% CI, 42.1 to 49.0) in the clarithromycin-hydroxychloroquine group, and 48.0 (95% CI, 44.4 to 51.2) in the placebo group (P = 0.08), a difference of 6.0 (95% CI, 2.4 to 9.6) in the doxycycline group vs. the placebo group and a difference of 3.0 (95% CI, 1.0 to 4.9) in the clarithromycin-hydroxychloroquine group vs. the placebo group; the score also did not differ significantly among the groups at subsequent visits (P = 0.05). In all study groups, the 9- to 16-week physical component summary scores increased significantly from baseline to the end of the treatment period (P < 0.001). The rates of adverse events were similar among the study groups. Four serious adverse events thought to be related to drug use occurred during the 12-week open-label corticosteroid phase, and no serious or related adverse event occurred during the 12-week randomized phase.

CONCLUSIONS

In patients with persistent symptoms attributed to Lyme disease, longer-term antibiotic treatment did not provide additional beneficial effects on health-related quality of life beyond those with shorter-term treatment (ClinicalTrials.gov number, NCT00137939).
Retrospective cohort study of 148 patients with polyclonal gammopathy


OBJECTIVE:
To quantify clinical conditions and laboratory values associated with moderate to marked polyclonal gammopathy.

PATIENTS AND METHODS:
Patient characteristics, laboratory correlates, evolving disease states, and survival of all patients seen at the Mayo Clinic, Rochester, Minn, during 1991 with a polyclonal gamma globulin level of 3.0 g/dL or higher were reviewed in this retrospective cohort study.

RESULTS:
One hundred forty-eight patients were identified (median age, 58 years; 59% female). In 130 patients (88%), only 1 diagnosis was identified. Liver disease was the most common single disease association in 79 (61%) of 130 patients, followed by connective tissue diseases in 28 (22%), chronic infections in 8 (6%), hematologic disorders in 6 (5%), and nonhematologic malignancies in 4 (3%). No difference in gamma globulin levels existed between groups. With a median follow-up of 67 months, 90 (63%) of 143 patients for whom follow-up was available were alive. By multivariate analysis, age, albumin concentration, disease group, and platelet count were predictive of survival. No patient developed myeloma or a clonal plasmoproliferative disorder.

CONCLUSION:
Moderate to marked polyclonal gammopathy may reflect an underlying condition: liver disease, connective tissue disease, hematologic disorder, infection, or malignancy.
Further history and investigations

- Swelling of the ankle, skin lesion and local pain since 2 months
- Pain increasing in the last few days
- Oral contraception since long time
- Protein S: 43% (normal: 59% - >120%)
  Protein C normal
Occlusive vasculopathy in protein S deficiency
Occlusive vasculopathy in protein S deficiency

- Hereditary (types I, II, III)
- Acquired (in vitamin K deficiency, warfarin treatment, chronic liver disease, some infections including HIV)
- Decreased protein S levels also in pregnancy and in women taking oral contraceptives
- Increased risk of venous thromboembolism
Protein S is a plasma protein that serves as a cofactor for the anticoagulant effects of activated protein C. Congenital protein S deficiency is associated with thromboph-embolic disease. During pregnancy, a decrease in the func- tional and antigenic levels of protein S occurs; this change in protein S status may contribute to the thromboembolic complica-tions that sometimes occur during pregnancy. In certain preg-nant patients, oral contraceptive use has also been associ-ated with thrombotic complications. In this study, pro-tein S status was determined in 21 women taking oral contraceptives and compared with that of 21 women not taking oral contraceptives and that of 21 men. The results show that women taking oral contraceptives have signifi-cantly lower total protein S (24.3 ± 3.8 ng/ml; mean ± SD) than women not taking oral contraceptives (29.8 ± 3.9 ng/ml; P < 0.05). Men had significantly higher protein S levels (30.9 ± 3.9 ng/ml; P < 0.01) than age-matched women not taking oral contraceptives. In plasma, an equi-librium exists between free (functionally active) protein S and protein S complexed to C4b-binding protein, which is functionally inactive. The mean levels of free protein S in women taking oral contraceptives and that of 21 men. The results showed that women taking oral contraceptives have significantly lower free protein S levels (11.8 ± 3.0 ng/ml; mean ± SD) than women not taking oral contraceptives (15.8 ± 2.3 ng/ml; P < 0.01). The reduced free protein S levels are accompanied by a significant reduction in total protein S antigen to 66% ± 11% (P < 0.001). Based on these data, we concluded that the changes in protein S status are among the factors that predispose pregnant women to thromboembolic complic-a-tions.

Since oral contraceptive (OC) use hormonally mimics pregnancy and has been associated with thrombotic compli-cations, we have evaluated OC users to determine whether signifi-cant changes in protein S status occur. Since sex hormonal differences could affect protein S levels, we have evaluated the protein S status of healthy males as well.

In normal individuals approximately 40% of protein S is found free in plasma, and 60% is complexed to C4b-binding protein (C4b-BP), an inhibitor of the complement system.1

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Hormonal Contraception and Thrombotic Risk: A Multidisciplinary Approach

The thrombotic risk is affected by estrogen dose, type of progestin, mechanism of delivery, and length of therapy. Oral progestin-only contraceptives and transdermal estradiol used for hormone replacement carry minimal or no thrombotic risk. Transdermal, vaginal, or intrauterine contraceptives and injectable progestins need further study.
Further history and investigations

- Clinical diagnosis of *Borrelia*-associated lymphocytoma cutis
- After the histological diagnosis of trichophytia, a culture demonstrated *Tr. rubrum*
Trichophytia with eosinophilic folliculitis

- Eosinophilic folliculitis represents a heterogeneous group of disorders, including:
  
  *) Eosinophilic pustular folliculitis (Ofuji)
  *) HIV-associated eosinophilic pustular folliculitis
  *) Pediatric eosinophilic pustular folliculitis
  *) Fungal and parasitic eosinophilic folliculitis
  *) Other (bacterial, after stem-cell transplantation)
M, 18

Cutaneous leishmaniasis
Further history and investigations

- No other skin changes; no involvement of the mucosae
- Sonography of abdomen and thorax-Rx normal
- Is being treated with photodynamic therapy
Cutaneous Leishmaniasis

- Leishmaniasis is becoming more frequent in non-endemic Countries due to travelers, refugees, troops stationed in endemic areas
- Europe: "old-world" leishmaniasis (L. tropica)
- Acute ("oriental boil", "Aleppo boil"), chronic (may mimic a variety of skin conditions), disseminated (anergic hosts)
Further history and investigations

- Hyperpigmented skin lesions since birth, partly along the Blaschko lines
- The out-patient chart does not mention the asymmetrical breast hypoplasia
Becker nevus syndrome

• Becker nevus in association with hypoplasia of the breast and/or other skin-related, muscular or skeletal defects (usually ipsilateral):

*) Absence of the pectoralis major muscle
*) Hypoplasia of ipsilateral subcutaneous fatty tissue
*) Hypoplasia of contralateral labium minus
*) Ipsilateral accessory scrotum
*) Underdevelopment of the muscles of the shoulder girdle
*) Scoliosis
*) Vertebral defects
*) Fused ribs
*) Ipsilateral shortness of a limb
*) Underdevelopment of the teeth and jaws
*) Sunken chest or abnormally prominent chest
*) Supernumerary nipples