Exacerbation of interstitial granulomatous dermatitis with arthritis by anakinra in a patient with diffuse large B-cell lymphoma

D. Michailidou, M. Voulgarelis, D. Pikazis

Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece.

Despina Michailidou, MD
Michalis Voulgarelis, MD
Dimitrios Pikazis, MD

Please address correspondence to:
Dimitrios Pikazis, MD,
Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, Mikras Asias 75 Street, Goudi, 11527 Athens, Greece.
E-mail: dpikazis@med.uoa.gr

Received on March 22, 2013; accepted in revised form on July 2, 2013.

Key words: interstitial granulomatous dermatitis, arthritis, anakinra, lymphoma

Competing interests: none declared.

ABSTRACT

Interstitial granulomatous dermatitis with arthritis (IGDA) is a rare idiopathic skin disorder with variable cutaneous expression, typically associated with a seronegative arthritis. Histopathology of this disorder reveals a granulomatous infiltrate with foci of collagen degeneration in the deep reticular dermis. We present a case of IGDA in a 56-year-old man with diffuse large B-cell lymphoma, exacerbated by the administration of anakinra.

Introduction

Interstitial granulomatous dermatitis with arthritis (IGDA) is an uncommon entity that primarily affects middle-aged women. It is characterised by variable cutaneous lesions and joint involvement (1). IGDA can be associated with several autoimmune systemic diseases (2), but its association with malignancy is not well established.

Case presentation

We report the case of a 56-year-old man who presented with intermittent fever, symmetric upper extremities arthritis, sore throat and a mild erythematous rash on his thighs one year before. His laboratory profile revealed at that time leucocytosis, raised erythrocyte sedimentation rate (86 mm/1sthour) and C-reactive protein (68 mg/l, normal values 0–6mg/l) and a slightly elevated serum ferritin level (328 ng/mL, normal values 20–300 ng/mL). Serological tests and blood cultures excluded common viral and bacterial infections. *Borrelia burgdorferi* and Parvovirus B19 serology, immunologic tests, tumour markers and PPD test were all negative. Two dimensional echocardiography and CT scan of the neck, chest and abdomen were normal.

At first, the patient was diagnosed as having adult-onset Still's disease (AOSD) fulfilling the Yamaguchi criteria. He had been intermittently treated with non-steroidal anti-inflammatory drugs (NSAIDs) and low methylprednisolone dose (6mg daily). Five months after the first evaluation, methotrexate 15 mg per week orally was added to methylprednisolone with partial remission of arthritis. Anakinra (Kineret®) 100 mg subcutaneously/day was added and, one week later, the patient presented in the emergency room of our department in apparent distress. On physical examination, temperature was 39ºC, symmetric polyarthritis of the small and large joints and multiple roundish erythematous papules and plaques on his posterior chest wall, buttocks and thighs were evident (Fig. 1). Besides, a 2cm right non-tender firm cervical lymph node, not present at the time of his first presentation to our department, the rest of the physical examination was normal. CT scan of the neck, chest and abdomen revealed multiple cervical lymph nodes 2cm in diameter occupying the right carotid and supraclavicular space.

In skin biopsy, mild perivascular inflammatory infiltrates of lymphocytes and eosinophils in the upper dermis and histiocytic infiltrates arranged interstitially and in palisades around degenerated collagen bundles were present in the lower dermis (Fig. 2). Lymph node biopsy revealed anaplastic variant of diffuse large B-cell lymphoma (DLBCL) with no evidence of clonal population in the cutaneous lesions (Fig. 3A, B). In particular the lymph node architecture was effaced due to the presence of very large round or polygonal lymphoid cells with bizarre pleomorphic nuclei and

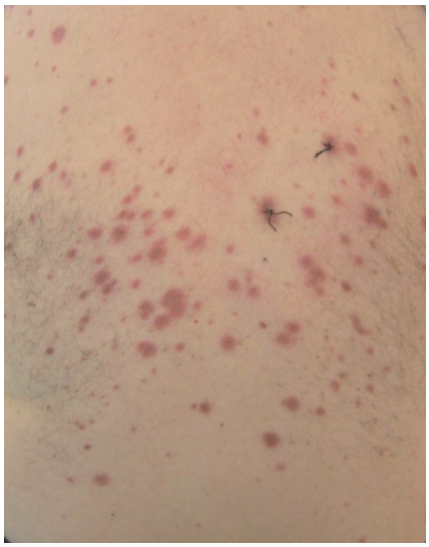


Fig. 1. Erythematous roundish, well-defined, smooth-surfaced, papules and infiltrated plaques symmetrically distributed on the posterior chest wall, ranging from 0.5 to 1 cm in diameter. (Stiches indicate the areas where punch skin biopsy was taken).

prominent nucleoli, resembling at least focally, anaplastic T-cell lymphoma. These cells showed a cohesive growth pattern, mimicking also an undifferentiated carcinoma. Immunohistochemical analysis showed that tumour cells were CD20+, CD79a+, PAX-5+, LCA+, bcl2+, CD10–, MUM-1+ and bcl 6+ (scattered positivity).

The clinicopathological findings were consistent with the diagnosis of IGDA and DLBCL. The patient received six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for lymphoma and both the cutaneous lesions and rheumatoid symptoms of IGDA resolved six months after the complete remission of his lymphoma.

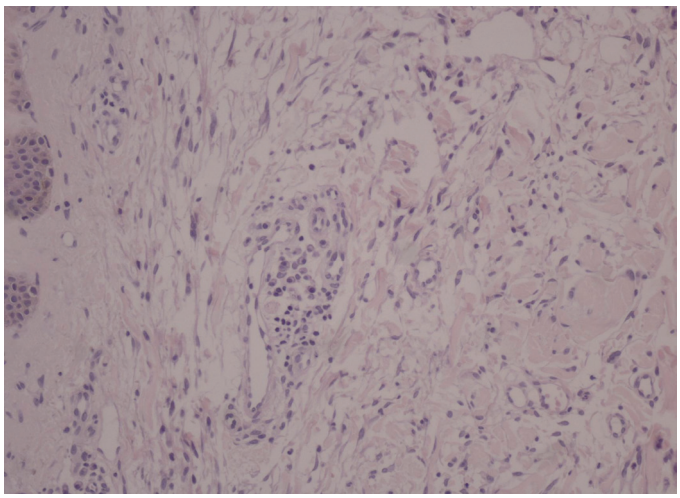
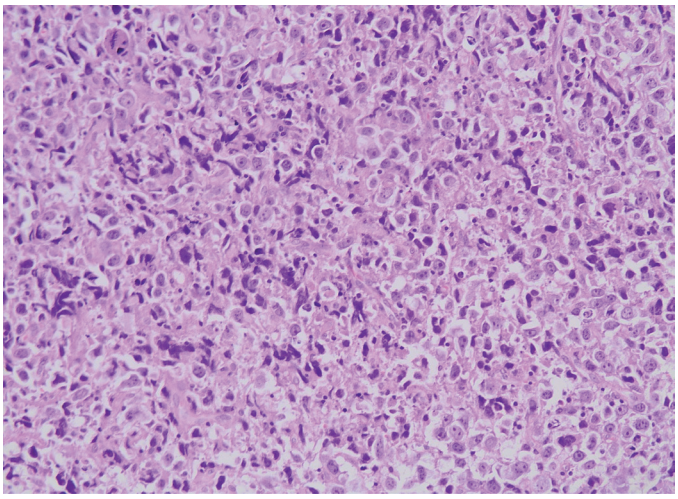


Fig. 2.
Interstitial lymphohistiocytic infiltrates with focal degenerated collagen bundles and giant cells are present in reticular dermis. Mucin (Alcian blue stain pH2.5) and direct immunofluorescence were negative. (Haematoxylin-eosin stain; original magnification ×200).



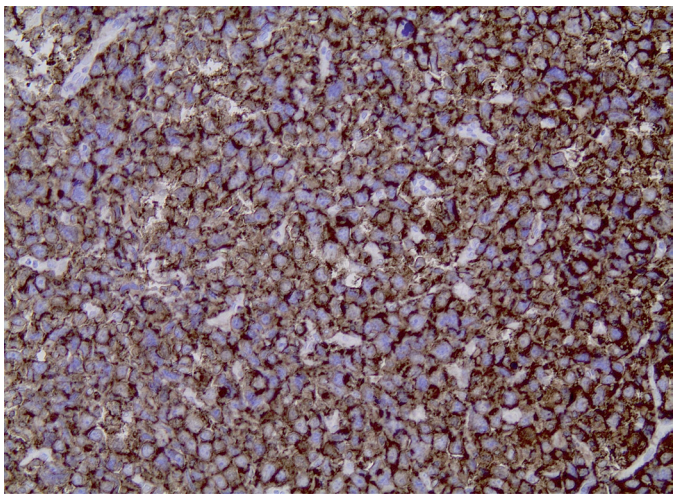


Fig 3. (Top)
Haematoxylin-eosin staining showing large lymphoid cells with highly pleomorphic nuclei and prominent nucleoli (HE X 400).
(Bottom)
Tumour cells show diffuse positivity for CD20 (x400).

Discussion

IGDA is a distinct entity for which a typical histological and clinical pattern is essential to establish diagnosis. The importance and the nature of the association with extracutaneous diseases needs to be clarified. Patients should be screened for rheumatic and autoimmune diseases (3).

In this case, IGDA could be considered a paraneoplastic manifestation of DLBCL, as the initial mild cutaneous lesions and joint symptoms preceded the manifestation of the lymphoma in our patient, an association that has not been previously described. IGDA might represent a cytokine-mediated systemic host-protective response against the tumour, with a non-specific strong stimulation of the immune system including histiocytes (4).

The introduction of anakinra therapy in our patient exacerbated the pre-existing cutaneous lesions and the joint manifestation of IGDA, probably due to its immune modulating effects. Our observation indicates that the suppression of interleukin-1 (IL-1) by anakinra may have induced an even greater imbalance among the inflammatory cytokines produced against the tumour cells, *i.e.*, IL-6, IL-1, TNF-α, with exacerbation of TNF-α and IL-6 mediated manifestations, such as granulomatous skin lesions, arthritis and fever. Anakinra has been shown to cause interstitial granulomatous drug reaction and in some other patients exacerbation of rheumatoid arthritis (5, 6).

The resolution of the of IGDA symptoms only after complete remission of the lymphoma, suggests either a cause and effective relation symptom or a serendipitous phenomenon.

Acknowledgements
We thank Professor H.M. Moutsopoulos, MD (Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens) for his instructive comments and suggestions.

References

1. BUSQUETS-PÉREZ N, NARVAEZ J, VALVERDE-GARCÍA J: Interstitial granulomatous dermatitis with arthritis (Ackerman Syndrome). *J Rheumatol* 2006; 33: 1207-9.
2. VERNEUIL L, DOMPMARTIN A, COMOZ F *et al*.: Interstitial granulomatous dermatitis with cutaneous cords and arthritis: A disorder associated with autoantibodies. *J Am Acad Dermatol* 2001; 45: 286-91.
3. PERONI A, COLATO C, SCHENA D *et al*.: Interstitial granulomatous dermatitis: a distinct entity with characteristic histological and clinical pattern. *Br J Dermatol* 2012; 166: 775-83.
4. RONGIOLETTI F, CERRONI L, MASSONE C *et al*.: Different histologic patterns of cutaneous granulomas in systemic lymphoma. *Dermatopathol* 2004; 51: 600-5.
5. REGULA CG, HENNESSY J, CLARKE LE *et al*.: Interstitial granulomatous drug reaction to anakinra. *J Am Acad Dermatol* 2008; 59: S25-27.
6. DEN BRODER AA, DE JANG E, FRANSSEN M *et al*.: Observational study of efficacy, safety, and drug survival of anakinra in rheumatoid arthritis patients in clinical practice. *Ann Rheum Dis* 2006; 65: 760-2.