Sir,
Rosai-Dorfman disease or sinus histiocytosis with massive lymphadenopathy (SHML) is characterized by non-malignant macrophagic proliferation within lymph node sinuses and extranodal sites. Histological analysis typically demonstrates macrophages exhibiting emperipolysis of lymphocytes (i.e. phagocytosis of lymphocytes by Rosai-Dorfman cells), and immunochemistry shows positivity for S-100 protein and negativity for CD1a (1–3). SHML is defined by painless, bilateral, cervical lymphadenopathy, associated with fever, leukocytosis, elevated erythrocyte sedimentation rate (ESR) and polyclonal hypergammaglobulinaemia (1, 3). Skin impairment is therefore one of the most common extra-nodal complications of the disease, occurring in 16% of patients (1, 3). Non-specific manifestations (macules, papules, plaques, subcutaneous nodules or soft tissue masses) are common, although skin involvement related to SHML may also mimic more rarely other cutaneous disorders, including lupus vulgaris, sarcoidosis and xanthoma (1, 3, 4). We recently observed a patient with SHML who developed granuloma annulare (GA) of both hands.

CASE REPORT
A 50-year-old woman, with unremarkable previous medical history, presented with a 1-month history of asthenia and fever. On admission, the patient was febrile (38°C) and physical examination revealed both bilateral and painless enlargement of cervical lymph nodes; general examination was otherwise normal. Laboratory studies disclosed the following: ESR 45 mm/h, haemoglobin 13 g/dl, leukocytosis 17 × 10⁹/l (70% of neutrophils), platelets 371 × 10⁹/l. Plasma glucose levels, as well as renal and liver tests, were normal. Blood protein electrophoresis showed hypergammaglobulinaemia; serum IgG level was increased: 22 g/l. Blood and urinary immune electrophoresis were normal. T-cell receptor-γ gene rearrangement, using PCR analysis and denaturing gradient gel electrophoresis, showed a monoclonal population of T cells in peripheral blood samples. Auto-antibody screening tests were negative for rheumatoid factors, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies and serum angiotensin-converting enzyme. Blood cultures, serological findings for bacteria (Chlamydia pneumoniae, Mycoplasma pneumoniae) and viruses (hepatitis viruses, cytomegalovirus, herpes simplex virus (HSV), human herpes virus 6 (HHV6), human immunodeficiency virus (HIV)) were negative; serological findings for Epstein-Barr virus (EBV) were as follows: serum antibody high titres IgG and no IgM. Histological examination of cervical lymph node tissues demonstrated numerous macrophages with abundant pale cytoplasm, exhibiting emperipolysis (Fig. 1a), and macrophages were positive for the S-100 protein (Fig. 1b) and negative for CD1a and CD20; neither bacteria nor parasites were detected by special staining, and EBV-encoded RNA was negative in the macrophages, as examined by in situ hybridization. Other investigations were carried out, including thoracic and abdominal computed tomography (CT) scan, as well as sternal bone marrow aspirate, which proved normal. Fluorine 18 (F-18) fluorodeoxyglucose positron emission tomography (PET-scan) showed a marked uptake of F-18 fluorodeoxyglucose in cervical lymph nodes (Fig. 2). A diagnosis of SHML without extra-nodal complications was made.

At 1 year follow-up, the patient presented with skin lesions of 3 months’ duration, i.e. annular plaques with indurated borders involving the back of both hands (Fig. 3). A skin biopsy specimens showed histological damage consistent with GA, i.e. multiple area of degeneration of collagen surrounded by palisading cells, these inflammatory cells being composed of epithelioid macrophages and few Langerhans’ cells and T cells; immunochemistry was negative for the S-100 protein and CD1. Stains and cultures of skin biopsy specimens for aerobic and anaerobic bacteria, mycobacteria and fungi were negative; studies to detect EBV RNA in skin were also negative. Auto-antibody screening tests were negative, particularly for rheumatoid factors and antinuclear antibodies. Serological...
findings for viruses were positive for EBV: high titres IgG and no IgM. Other tests, including thoracic and abdominal CT scan, were within normal limits.

DISCUSSION

GA is a benign dermatosis of unknown origin, characterized by pale and erythematous papules grouped in rings or arch figures (5, 6). It has usually been associated with various chronic conditions linked to immune dysfunction, including infectious disorders (such as herpes varicella-zoster virus, HSV, EBV, HIV), auto-immune diseases (especially diabetes mellitus and auto-immune thyroiditis) and malignancies (Hodgkin’s disease, T- and B-cell lymphoma, chronic myelomonocytic leukaemia, myelodysplastic syndrome or carcinoma) (5–10).

Scheel et al. (4) have described previously a case of a patient with extranodal SHML presenting as giant GA-like lesions (5). To our knowledge, this is the first report of a case of GA involving both hands in a patient with SHML without extranodal involvement. Moreover, PET-scan provided detailed evidence of SHML-related lymph node involvement. The pathological mechanisms of GA in our patient with SHML remain unclear, which raises the question of whether the condition arose through a causal association (as part as a continuum) or by chance. Taken together, we suggest that two pathophysiological mechanisms may be involved. Firstly, as GA is encountered in patients with cell-mediated immune disorders (9), GA may also be due to acquired immune dysregulation of T cells related to SHML in our patient. In essence, patients with SHML have a cellular immune dysregulatory process, which has been evidenced by: (i) the histological damage revealing lesional cell derivation from circulating mononuclear cells (macrophages, Langerhans’ cells, T cells) (11); and (ii) the presence of a defect in circulating lymphocytes with a reversed CD4/CD8 ratio as well as decreased lymphocyte mitogenic responses in patients (1, 12). The presence of a clonal T-cell population in blood samples of our patient with SHML suggests T-lymphocyte impairment, as clonality of T cells is more commonly encountered in diseases involving T-cell lineage (13). Secondly, a causative relationship between onset of both SHML and GA and infectious micro-organisms (particularly EBV and HHV6) may be speculated (1, 3, 14, 15). In small series, in situ DNA hybridization within biopsy specimens has demonstrated the HHV6 genome in macrophages in 78% of patients with SHML (1, 15); moreover, high titres of EBV antibodies have been found in patients with SHML and GA (3, 14). In this instance, our patient with both SHML and GA exhibited high titres of EBV IgG; however, microscopic studies of both cutaneous and lymph node tissues did not disclose pathogen micro-organisms in skin and lymph node sections. Admittedly, serological tests alone are not conclusive for an aetiological role of EBV in our patient. The recognition of GA should alert physicians, to the possibility that other underlying disorders are involved, including cell-mediated immune disorders.

REFERENCES

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Letters to the Editor

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