Erythema elevatum diutinum is a rare neutrophilic dermatosis, which presents as persistent, symmetrical, purple or brownish papules and nodules, mainly in the extensor surface of the limbs.

We describe a case of erythema elevatum diutinum and polyarthritis as initial manifestations of Crohn’s disease associated spondyloarthritis.

A 51-year-old man, from São Tomé e Príncipe, with previous history of treated tuberculosis and chronic hepatitis B infection, was admitted due to 4 months history of polyarthritis, hyperpigmented papules on the extensor surfaces, occasional episodes of bloody mucous diarrhea and significant weight loss. Histology of the skin showed myeloperoxidase positive neutrophilic granulocytes with moderate karyorrhexis, consistent with erythema elevatum diutinum. Colonoscopy showed erosions in sigmoid and rectum.

Diagnosis of erythema elevatum diutinum secondary to Crohn’s disease with associated peripheral spondyloarthritis was assumed. The patient was treated with prednisolone, sulphasalazine, metronidazole, azathioprine and tenofovir with good clinical response.

As erythema elevatum diutinum can be secondary to multiple systemic diseases, including rheumatic diseases and inflammatory bowel disease, being aware and recognizing this entity can be of great importance for rheumatologists.

Keywords: Erythema elevatum diutinum; Crohn’s disease; Spondyloarthritis; Cutaneous vasculitis.

INTRODUCTION

Erythema elevatum diutinum (EED) is a rare neutrophilic dermatosis, first described by Hutchinson in 1888, that has been considered a variant of leukocytoclastic vasculitis. It has no racial predilection and it can occur in any age, though it is most common between the fourth and sixth decades of life.

EED often presents as persistent, symmetrical, firm, tender, red or purple papules and nodules that may coalesce to form larger nodules or plaques. The extensor aspects of the extremities, near joints, are the preferred location for skin lesions.

The cause of EED is unknown, but it has been hypothesized that EED is mediated by immune complexes deposition in the perivascular dermis that induce an inflammatory response which in turn damages the vessel walls, resulting in fibrosis. It has been described as associated with neoplasms, infections (Streptococcus, hepatitis B (HBV) and C (HCV) virus, human immunodeficiency virus (HIV)), rheumatic diseases (rheumatoid arthritis (RA), lupus erythematosus), inflammatory bowel diseases (ulcerative colitis, Crohn’s disease, celiac disease) and other conditions.

The differential diagnosis of EED comprehends mainly Sweet syndrome, pyoderma gangrenosum, granuloma annulare, Kaposis sarcoma. Skin biopsies are the mainstay of the diagnosis, allowing differential diagnosis to be excluded.

First-line treatment is to target underlying systemic conditions. Other treatment options are limited, with dapsone being the most commonly used agent.

We describe a case of EED and polyarthritis as ini-
tial manifestations of Crohn’s disease, to raise awareness to this rare form of leucocytoclastic vasculitis, as an accurate diagnosis can prompt the investigation of underlying conditions.

CASE REPORT

A 51-year old black man was admitted to the Rheumatology Department, on July 2013, for diagnostic investigation of arthralgia, cutaneous lesions and weight loss.

The patient had lived in São Tomé e Príncipe until December 2006. He had a previous history of pulmonary tuberculosis (TB) infection treated with multiple antibacillary drugs. He was then submitted to left inferior lobectomy and his condition improved, only with mild cough persisting after surgery. In 2009, an incidental diagnosis of chronic HBV infection was performed. At the time, hepatic enzymes were normal.

On admission, the patient reported a four months history of symmetric, additive, inflammatory arthralgia in small joints of the hand, wrists, elbows, knees and ankles, with good response to nonsteroidal anti-inflammatory drugs (NSAIDs). One month after the beginning of these symptoms, non-pruritic cutaneous lesions on the arms and feet appeared. At the same time, the patient recalled having occasional episodes of bloody mucous diarrhea and had lost 16% of total body weight.

His physical exam was remarkable for hyperpigmented papules on the extensor surfaces of the metacarpophalangeal and proximal interphalangeal joints (Figure 1A), and purpuric lesions with ulcerations on the soles (Figure 1B), elbows and digital pulps, legs and buttocks (Figure 1C), symmetrical polyarthritis (PIPs, MCPs, wrists, knees and ankles), muscle wasting, a systolic murmur on the aortic focus and hepatosplenomegaly. The neurological exam was normal.

His laboratory workup was noteworthy for elevated erythrocyte sedimentation rate (ESR, 120mm/1st h, normal (N) <20) and C-reactive protein (CRP, 2 mg/dL, N <0.5), normocytic anaemia (hemoglobin, 11.7g/dL, N >13.0), mild eosinophilia (970 cells/µL, N <500), prolonged prothrombin time (INR 1.3), slight elevation of aspartate transferase (AST 45U/L, N<32) and normal alanine transferase (ALT, N<32), polyclonal hypergammaglobulinemia (gamma fraction 3.21 g/dL, N: 0.4-1.5) and very high viral load (DNA HBV

FIGURE 1. Hyperpigmented papules on the extensor surfaces of the metacarpophalangeal and proximal interphalangeal joints (A) and purpuric lesions on the soles (B). Cutaneous papules and nodules with ulceration affecting the buttocks (C, left) and anterior surface of the legs (C, right). Fine enthesophytes on the insertion of the tricipital and quadricipital tendons (D).
He had positive anti-citrullinated protein antibodies (ACPA, titre 40.2 U/L, N<20) and equivocal anti-double stranded DNA antibodies (anti-dsDNA, titre 221.6, N<200). Rheumatoid factor (RF, N<16 U/mL), anti-neutrophil cytoplasmic antibodies (c-ANCA, p-ANCA, both N<20 UI/mL), antinuclear antibodies (ANA, N<1/160), human leukocyte antigen (HLA) B27 and serum cryoglobulins were negative. Angiotensin converting enzyme was also within normal limits. A myelogram was performed, showing an eosinophil increase (12% of total cell population, N<6%), hypocellularity, with shift of the myeloid/erythroid ratio in favor of the granulocytic series.

A thorough investigation was conducted to exclude an infectious cause. Bacteriological and mycobacteriological exams of blood, urine and stool were negative. Parasitological exam of the stool was also negative. Bronchofibroscopy showed tracheomalacia and bronchoalveolar lavage was unremarkable, with negative bacteriological and mycobacteriological exams.

Multiple cutaneous biopsies of the skin lesions, in various locations, were performed. Gram, periodic acid-Schiff (PAS) and Grocott staining, as well as bacteriological and mycobacteriological exams, including Mycobacterium leprae, were negative. Immunohistochemistry (anti-leishmania, anti-mycobacterium tuberculosis) was also negative.

Transesophageal echocardiography excluded the presence of vegetations and determined mild aortic insufficiency. A whole-body computerized tomography showed no images suggesting tumoral lesions or sources of occult infection. A liver biopsy was performed, showing mild to a moderate mononucleated inflammatory infiltrate, portal and acinar fibrosis, focal hepatocellular necrosis, interface hepatitis and significant staining for HBV markers. HBV infection treatment was initiated promptly with tenofovir (300mg/day).

Articular ultrasound confirmed polyarticular synovitis, no erosions found. Radiographs (including the axial skeleton) showed no structural damage. Fine enthesophytes were found bilaterally on the insertion of the tricipital and quadricipital tendons (Figure 1D).

On electromyography (EMG), low sensitive action potentials were found in the right ulnar, peroneal and sural nerves, with no changes in the motor component. Sural nerve biopsy revealed asymmetric inflammatory infiltrate in both nerve and vessels, suggesting vasculitic neuropathy.

Colonoscopy showed erosions in sigmoid and rectum, which histologically corresponded to undetermined inflammatory bowel disease (IBD) findings (moderate diffuse lamina propria lymphoplasmacytic infiltrate with lymphoid aggregates, basal plasmacytosis, criptitis, erosions and one non-necrotizing granuloma), with mild activity (Figure 2). Duodenum biopsies exhibited an intense lymphoplasmacytic infiltrate, with epithelial regeneration and some areas of atrophy.

The anatomopathological study of skin lesions showed, on the medium and reticular dermis, a high number of myeloperoxidase (MPO) positive perivascular neutrophilic granulocytes and some eosinophils with massive karyorrhexis, but without blood extravasation or fibrinoid deposits associated. Advanced lesions showed slight dermal fibrosis. Nuclear endothelial marker – ERG and CD31 staining demonstrated the presence of many capillary vessels (Figure 3).

After clinical correlation, these findings established the diagnosis of erythema elevatum diutinum (EED), assumed to be associated to Crohn’s disease with peripheral spondyloarthritis. The patient was treated with prednisolone (PDN) 1mg/Kg/day, sulphasalazine 2g/day and metronidazole 1000mg/day. A good clinical response followed and the patient became asymptomatic within 16 weeks, with significant improvement of the cutaneous lesions (regression of the lesions to cicatricial changes) and weight gain. Steroids were then tapered until 0.5mg/Kg/day of PDN. At this dose, the patient experienced muco-bloody diarrhea and...
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monoa rthritis of the tibiotalar joint. Azathioprine was added with improved disease control and no relapse of skin or joint involvement, and allowing further steroid tapering. Steroids were discontinued after a year without disease relapse. Antiviral treatment for hepatitis B was effective, with significant decrease of viral load after 12 months (3723 UI/mL, log_{10} 3.57).

**DISCUSSION**

_Erythema elevatum diutinum_ is an inflammatory dermatosis, characterized by a neutrophilic infiltrate of the dermis in the absence of cutaneous infection. In the present case, we found an intense infiltrate of polymorphonuclear cells (MPO+) with moderate karyorrhexis and with older lesions showing fibrosis. The absence of blood extravasation and the presence of late-stage lesions showing fibrosis is characteristic of classic EED and allow the distinction among other forms of leukocytoclastic vasculitis. Other neutrophilic dermatoses (such as Sweet syndrome) are rarely associated with vasculitis, and some are associated with granulomatous inflammation (e.g. *granuloma annulare*), absent in EED.

The clinical presentation of EED in our patient showed typical aspects (painless, non pruritic brownish and purpuric nodules and papules in extensor surfaces of the limbs) and more atypical features, such as the presence of ulcerations in elbows, buttocks and legs.

EED was reported to be associated with numerous pathologies, including rheumatic diseases, viral infections and inflammatory bowel disease. In the present case, the initial clinical picture with symmetric polyarthritis, elevated CRP and ESR and low-titer ACPA positivity could point to RA. However, the presence of muco-bloody diarrhea along with endoscopic and histologic documentation of intestinal inflammation, affecting both duodenum and colon, concurred to Crohn’s disease (although with only a single granuloma identified in the colon tissue sample). Moreover, intestinal, cutaneous and articular manifestations occurred almost simultaneously. Also, enthesopathy, as observed in our patient, is a common feature of spondyloarthritis and no bone erosions were found in joint radiography or ultrasound. Overall, a diagnosis of Crohn’s disease with associated polyarthritis was assumed as more likely. Immunosuppressive treatment was started with global improvement. Corticosteroid tapering was followed by disease relapse (abdominal pain, diarrhea and monoarthritis of the ankle), a clinical picture that is actually more characteristic of Crohn’s disease with associated spondyloarthritis.

Thus, both polyarthritis and EED seem less likely to be associated chronic infection with HBV, serologically detected several years before. In addition, as mentioned above, the relapse of the disease occurred when a decrease in viral load had already been documented. Nevertheless HBV infection could also be a possible trigger for EED. Although in this case HBV infection was diagnosed long ago, and apparently then there were no systemic manifestations of the hepatic disease.

Peripheral sensitive neuropathy diagnosed in this patient was subclinical, the onset being impossible to date. EMG was previous to treatment with metronidazole, a recognized neurotoxic drug. Active chronic hepatitis B could cause peripheral neuropathy by vas-

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**FIGURE 3. Erythema elevatum diutinum** presenting with the histopathological pattern of chronic leukocytoclastic vasculitis, showing marked fibroplasia, in conjunction with perivascular neutrophilic granulocytes and massive karyorrhexis (A). Distinctive myeloperoxidase-positive neutrophilic aggregates (C) with pronounced karyorrhexis, but without significant erythrocyte extravasation (B). Moderate capillary proliferation with ERG-positive endothelia (D).
cular involvement (vasculitis) or direct immune-mediated damage. In accordance, our patient's nerve biopsy revealed an intense infiltrate of T lymphocytes in both vessel and nerve. However, it is difficult to exclude other etiologies for the neuropathy, such as Crohn's disease itself. Peripheral neuropathy has also been reported in association with Crohn's disease although it occurs more commonly in ulcerative colitis.

Mild peripheral eosinophilia and central non-clonal eosinophilia was documented. However, eosinophilic infiltration in all the tissues sampled was never found and other common manifestations of idiopathic hypereosinophilic syndrome were absent. Reactive forms of eosinophilia are far more common than primary forms and include inflammatory bowel disease.

EED lesions almost disappeared after initiation of sulphasalazine, high-dose prednisolone and metronidazole. Dapsone remains the treatment of choice for EED. This option has limitations since dapsone is a suppressive rather than curative therapy, and withdrawal usually results in prompt and severe recurrence of disease. As in other neutrophilic dermatoses, sulphapyridine has shown similar effects as dapsone. Sulphasalazine, being a compound derived from sulphapyridine, may be in part responsible for the cutaneous improvement. Also, treatment of the underlying condition is associated with an improvement of the EED lesions.

To the best of our knowledge, the association between EED (per se, an uncommon vasculitis) and Crohn's disease has been previously reported in only 3 cases in literature. This case illustrates a complex investigation that has led to an unexpected diagnosis. As erythema elevatum diutinum can be associated with multiple diseases, including rheumatic diseases and IBD, being aware and recognizing this entity can be of great importance for rheumatologists.

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