Atypical Rheumatoid Nodules: A Possible Precursor to a Rheumatoid Variant in a Rheumatoid-Factor-Negative Patient. Case Report

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Abstract Subcutaneous nodules occur in approximately 20–25% of rheumatoid factor (RF)-positive rheumatoid patients. In this paper, we present a unique case of a 47-year-old healthy RF-negative woman with a 3-year history of necrobiotic nodules over the dorsum of her hands, extensor forearms, and lower extremities. This may represent an atypical presentation or a new rheumatoid variant.

Keyword Rheumatoid nodules

Introduction

Subcutaneous rheumatoid nodules occur in approximately 20–25% of patients with rheumatoid arthritis (RA) and are universally associated with positive rheumatoid factor (RF). These tender nodules are typically found over the olecranon and extensor surface of the forearm and the dorsal and palmar surfaces of the hands. Their appearance usually coincides with systemic disease and joint symptoms. However, reports exist of pulmonary necrobiotic rheumatoid nodules preceding the onset of RA [3, 6, 7, 9, 11].

Necrobiotic nodule is a histopathologic term characterizing a nodule with a central region of fibrinoid necrosis (necrosed collagen), a middle region consisting of a palisade of elongated histiocytic cells, and an outer region of granulation tissue with fibrosis, plasma cells, lymphocytes, and possibly giant cells [8]. Within the differential is a rheumatoid nodule, subcutaneous granulomas annulare

(SGA), and necrobiosis lipoidica. SGA is a benign inflammatory skin lesion most frequently found in the pre-tibial region, ankle, and scalp [4] without other organ involvement. Cases of isolated hand involvement with SGA are rare. A diagnosis of necrobiosis lipoidica is made in the clinical setting of diabetes mellitus (DM).

Although it appears possible to differentiate necrobiotic rheumatoid nodules from SGA on histology [10], this can be exceedingly difficult. Despite this difficulty, the definitive diagnosis of a rheumatoid nodule can usually be made using supportive clinical evidence of other RA criteria. In this paper, we present a unique case of a 47-year-old healthy RF-negative woman with a 3-year history of nodules over the dorsum of her hands, extensor forearms, and lower extremities but lacking any clinical symptoms of RA. To our knowledge, this is the first reported case of rheumatoid nodules in a RF-negative patient without joint involvement and may represent an atypical presentation or a new rheumatoid variant.

Case

A 47-year-old right-hand-dominant female gardener of exotic plants presented to our clinic with a 3-year history of smooth annular papular-like plaques over the dorsum of the metatarsophalangeal (MP) joints of both hands, dorsal forearms, and posterolateral lower extremities (Fig. 1). She is a non-smoker with no significant past medical history or medication use.

The lesions had a gradual onset with no history of trauma and foreign body. Each successive lesion was tender with its initial appearance, but this subsided over the following months. The lesions were non-scaly and non-pruritic. There was no evidence of systemic illness, fevers,

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Figure 1 Smooth annular popular-like plaques over the dorsum of the MP joints of both hands.

cough, and no reports of joint pains. One of the dorsal hand lesions had been previously excised and had not recurred.

On examination, the lesions were non-tender, linear multi-focal nodules. There was a yellowish/white hue within the subcutaneous tissue. The nodules appeared to be somewhat adherent to the underlying extensor tendons. However, the patient demonstrated a full range of motion of the hands and wrists. In addition, she was noted to have fullness on the volar aspect of the distal forearms ulnarly. These areas were non-tender but again appeared to be adherent to the underlying flexor tendons and were seen to move with wrist and finger flexion.

Plain radiographs were unremarkable with no evidence of calcification or joint changes. Magnetic resonance imaging (MRI) demonstrated enhancing synovitis surrounding all of the individual extensor compartments, most marked surrounding the extensor carpi ulnaris and the first and second extensor compartments (Fig. 2). To a lesser degree, this synovitis involved the flexor tendons proximal to the carpal tunnel.

Serologic investigations were exhaustive. No evidence was found for gout, diabetes mellitus, viral or other infectious etiologies, hypercholesterolemia, or elevated triglycerides. Alkaline phosphatase, white blood cell count, erythrocyte sedimentation rate, and C-reactive protein were all within normal limits. All rheumatologic assays were non-contributory. A negative computed tomography (CT) scan of the abdomen and pelvis ruled out an occult malignancy and made a paraneoplastic syndrome unlikely.

The patient was taken to the operating room for excisional biopsy of a dorsal MP nodule, underlying joint synovium, and volar wrist synovitis (Figs. 3, 4, and 5). The appearance of all tissues was that of a chronic inflammatory type synovial proliferation circumferentially enveloping and adhering to the flexor tendons at the wrist similar to a

Figure 2 Enhancing synovitis surrounding all of the individual extensor compartments and involving the flexor tendons proximal to the carpal tunnel.

rheumatoid synovitis, except for the granular/gritty feel of the tissue. Postoperative healing was uneventful.

A diagnosis of necrobiotic nodules was made on general pathology with no evidence of amyloid. Specific dermatopathology findings were that of areas of palisading granulomatous inflammation consisting of fibrinoid necrobiosis (red with Masson trichrome) surrounded by histiocytes in a palisading array (Fig. 6). Mucin deposition was present in areas of necrobiosis (Fig. 7). This led to a differential diagnosis of rheumatoid nodule, SGA, and necrobiosis lipoidica.

The patient was not diabetic, excluding necrobiosis lipoidica. Preoperative rheumatologic assessment included a routine chest radiograph, which revealed light interstitial change in the bases suggesting fibrosis. She went on to have pulmonary function studies, which were within normal limits. A CT scan of the chest revealed scattered

Figure 3 Intraoperative appearance of dorsal MP nodule.

Figure 4 Intraoperative appearance of thickened synovial-like tissue of volar wrist.

ground-glass appearance with mild associated septal thickening in the periphery of both lung bases most suggestive for early or mild interstitial lung disease. It was felt that this was consistent with seronegative rheumatoid-like pulmonary manifestations. Taken together with the inconsistencies between our patients' presentation and that typical of SGA, a presumptive diagnosis of necrobiotic rheumatoid nodules and tenosynovitis in a RF-negative patient with early pulmonary interstitial disease was made. A trial of anti-tumor necrosis factor therapy (etanercept) was initiated, and the patient will be followed with serial pulmonary examinations.

Discussion

The differential diagnosis of a necrobiotic nodule includes rheumatoid nodule, SGA, and necrobiosis lipoidica. As each of these conditions has a distinctly different treatment and failure to make an accurate diagnosis could lead to serious sequelae, distinguishing among them becomes essential. Reliance on histology to make this distinction can be complicated.

Figure 5 Intraoperative appearance after volar tenosynovectomy.

Figure 6 Necrobiotic nodules with areas of palisading granulomatous inflammation consisting of fibrinoid necrobiosis surrounded by histiocytes in a palisading array.

Patterson performed a histochemical study on 12 cases of rheumatoid nodules and nine cases of SGA in an attempt to distinguish the lesions [10]. Rheumatoid nodules tended to show homogeneous, eosinophilic necrobiosis, giant cells within palisaded foci and significant stromal fibrosis, while SGA lesions demonstrated pale, edematous necrobiosis, an absence of giant cells, and lesser degrees of fibrosis. The single most useful differentiating feature was alcian blue

Figure 7 Mucin deposition was present in areas of necrobiosis as seen with Alcain blue stain.

stain for mucin, which was positive in all cases of SGA but only one case of rheumatoid nodule. Interestingly, this single case was in the only patient with seronegative arthritis.

Because the histochemical features of necrobiotic nodules are variable and do not always permit differentiation, the patients' clinical picture becomes essential in making the diagnosis. We present a case of necrobiotic nodules where the clinical picture did not readily lead to diagnosis. Moreover, when the diagnosis was made, the presentation of disease was atypical.

Our patient was a healthy 47-year-old woman with no systemic complaints or joint pain. She presented with a 3-year history of painless linear arrays of nodules over the dorsum of her MP joints, extensor forearms, and lower extremities. Initial suspicions of cholesterol or gouty deposits were not substantiated. Similarly, infectious and metabolic etiologies were ruled out as were paraneoplastic syndromes.

Examination and MRI indicated, in addition to the subcutaneous nodules, a peritendinous thickening about the volar aspect of the wrists. Biopsies of both nodules and volar fibrinous tissue revealed necrobiotic nodules consistent with the reported histochemical features typical of rheumatoid nodules [10].

However, our patient did not present with classic features of RA as seen in those patients reviewed by Patterson. Within his study, all RA patients met American Rheumatology Association criteria. The mean patient age was 56. The mean age for the SGA group was 19 years; none had a history of arthritis or related symptoms, and lesions were not found deeper than the mid-dermis [10]. In another review of 7 patients with SGA of the hand, the average patient age was 37 [5]. The presentations were that of one or two painless lesions of the dorsal hand, most commonly over the MP joint. Thus, clinically distinguishing features of SGA are its earlier age of onset in the first three decades of life, its tendency to spontaneously resolve, and absence of other symptoms [5]. SGA has been linked to persistent trauma or scarring [1], stressful life events [13], or a previously undiagnosed malignancy [2].

Initially, SGA was a consideration for our patient, as she had no other presenting complaints; yet, her peritendinous tissue and advanced age made a diagnosis of necrobiotic rheumatoid nodules more likely. Moreover, the presence of mucin seen in her biopsy is consistent with the RF-negative patient in Patterson's series [10]. This, taken together with the incidental finding of interstitial lung disease, strengthened our suspicion of an atypical presentation of RA or a novel rheumatoid variant.

Although there are no reported cases of necrobiotic subcutaneous rheumatoid nodules of the hand, as the initial presentation of RA in RF-negative patients, pulmonary necrobiotic nodules have been the initial and isolated symptom [3, 6, 7, 9, 11]. The most common pulmonary manifestations of RA are pleural adhesions, effusions, and fibrosing alveolitis [12], whereas necrobiotic nodules are rare. Nodules can vary in size and number and can precede other features of RA by several months to years. The presence of RF in these cases was variable, tending to be more prominent in those patients who went on to develop significant joint involvement.

Our patient presented with multiple necrobiotic subcutaneous nodules in the absence of joint or other systemic symptoms. Incidental pulmonary findings supported the diagnosis of RA. We believe this to be the first reported case of RF negative condition with rheumatoid nodules as the presenting feature and may represent a new rheumatoid variant.

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