SCIENTIFIC LETTER

A woman with rheumatoid arthritis,cavitary pulmonary nodules and skin ulcer

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Introduction

Rheumatoid arthritis (RA) more often affect women, but extra-articular manifestations – cardiac, cutaneous, gastrointestinal, nervous, ocular, pulmonary and renal, are predominant in men [1–7]. These changes are found in approximately 40-50% of active chronic disease [1, 5, 6, 8]. Skin nodules occur in up to 20% of cases, mainly if rheumatoid factor is positive [1-3, 5], and are related to small vessel vasculitis, similarly to digital changes and ulcers of extremities. Pulmonary nodules are associated with positive rheumatoid factor and anti-cyclic citrulinated peptide antibody; and can evolve with necrosis and central cavitations [1-3, 5-7]. The woman herein reported had longstanding seropositive RA with cavitary pulmonary nodules and indolent cutaneous ulcer in the left elbow.

Case report

A 65-year-old woman was admitted on April 2014 with heart failure and sequels of RA that was diagnosed five years ago. She was undergoing treatment with methotrexate in the last two years. In spite of a negative tuberculin test, because of a suspicious pulmonary image on the left upper lobe she empirically used isoniazid, rifampicin, ethambutol, and pyrazinamide till January 2014. More recently, there was a right olecranon bursitis associated with a local well demarcated ulcer, and methotrexate was changed by hydroxychloroquine and prednisone; without clinical response. Despite of these medications plus local surgical procedures, her elbow ulcer persisted opened; moreover, left pleural effusion developed in association with bilateral pitting edema in the lower limbs. She was a heavy smoker (40 pack years) and denied exposure to environments with silica or asbestos. Co-morbidities were osteporosis, type 2 diabetes mellitus, and high blood pressure.

Physical examination showed BMI 24.26 kg/m^2, spO2 92%, 36° C, 88 bpm, 130/80 mmHg, reduced lung sounds in the left medium third and fine rales in apical areas; there was also wrist deviation and typical hand changes of RA, pretibial purpura and elbow ulcer (**figure 1**), but no subcutaneous nodules. Routine laboratory determinations on admission and respective controls are compared in **table 1**. Thyroid function evaluation (normal ranges in parenthesis) showed TSH (0.27-5.0) 2.78 mcIU/mL, free-T4 (0.93-1.7) 1.21 ng/dL, anti-thyroperoxidase (<35) 8.49 IU/mL, and anti-thyroglobulin (<115) 16.31 IU/mL. In addition to positive rheumatoid factor, imunological tests revealed C3 complement (90-180) 74.9 mg/dL, C4 complement (10-40) 9.55 mg/dL, anti-DNA (<20) 7.0 IU/mL, ANA-HEp-2 positive 1:80 with nuclear fine speckled pattern, and anti-cyclic citrullinated peptide (<5.0) 85.0 U/mL. Arterial blood gas revealed pH 7.43, pCO_2 48.5 mmHg, pO_2 48 mmHg, $cHCO_3$ 32.2 mmol/L, tCO_2 65 mmol/L, cBase 7.8 mmol/L, sO_2 79.7%, anion Gap 13.4 mmol/L, and ctO_2 13.4 mmol/L. Chest radiography and computed tomography showed left pleural effusion, and bilateral cavitary nodules (**figure 2**).

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Biopsies by thoracocentesis and bronchoscopy were done; and microbiologic and histopathologic evaluations ruled out pulmonary malignancies, as well as infections by fungi, bacteria, or mycobacteria. Pleural fluid evaluation showed glucose 123 mg/dL, LDH 162 U/L, amylase 10 U/L, cholesterol 22 mg/dL, triglycerides 19 mg/dL, total protein 1.82 g/dL, albumin 0.88 g/dL, red cells 9,360/ mm^3, nucleated cells 40/mm^3 (polymorphonuclear 83% and mononuclear 15%); microbiological tests were negative, and malignant cells were not detected. She underwent pulse therapy with methylprednisolone 750 mg/day for three days. During hospitalization she used the following medications - enalapril, acetyl salicylic acid, furosemide, prednisone, carvedilol, sitagliptin, aledronate, calcium, vitamin D, fluticasone plus salmeterol, in addition to insulin. Control determination of arterial blood gas showed pH 7.43, pCO_2 48.6 mmHg, pO_2 75 mmHg, $cHCO_3$ 32.2 mmol/L, tCO_2 64 mmol/L, cBase 7.8 mmol/L, sO_2 96.3%, anion gap 16.2 mmol/L, and ctO_2 16.4 mmol/L. With exception of the cutaneous elbow ulcer (**figure 1 D**), there was good clinical recovery, and she was referred to follow-up in outpatient Rheumatology service.

Table 1. Routine tests of a 65-year-old woman with rheumatoid arthritis and lung nodules.

Parameters (normal ranges)	D1	D7	D24	D35
Erythrocytes (4.7-6.0 x 10^{12}/L)	5.45	5.01	4.54	5.04
Hemoglobin (13.5-18 g/dL)	13.7	12.3	11.2	12.5
Hematocrit (42-52%)	44.9	40.2	35.2	40.8
Leukocytes (4-11 x 10^9/L)	8.19	9.13	13.72	6.54
Neutrophils (40-73%)	78	79	87	77
Platelets (> 150 x 10^9/L)	218	184	172	149
Erythrocyte sedimentation rate (< 20 mm/ h)	18	21	24	-
C-reactive protein (< 0.8 mg/dL)	1.5	0.6	0.3	0.2
Sodium (135-145 mEq/L)	143	136	139	136
Potassium (3.5-5.2 mEq/L)	4.5	5.1	4.0	4.9
Urea (10-50 mg/dL)	52.2	51.8	75.7	38.2
Creatinine (0.7-1.2 mg/dL)	0.8	0.7	1.2	1.2
Albumin (3.5-5.2 g/dL)	3.5	-	3.3	-
Globulin (2.5-3.0)	2.8	-	2.9	-

D: day of hospitalization (admission on April 13 and discharge on May 18, 2014).

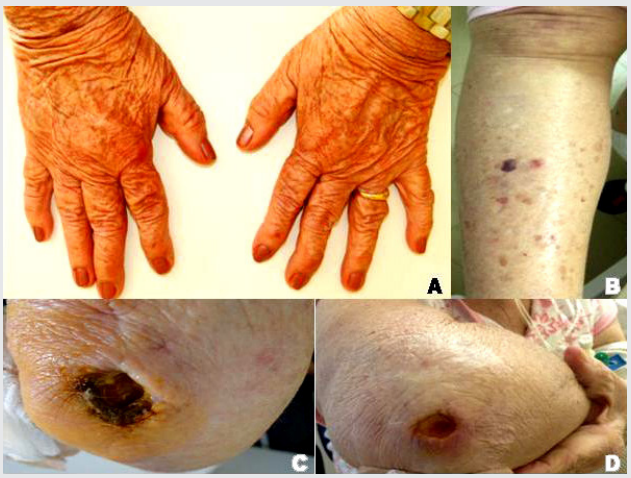

Figure 1. A) Classical features of chronic rheumatoid arthritis, including the subluxation of metacarpophalangeal joints, changes of proximal and distal interphalangeal joints, in addition to bilateral stiffness and swan neck and boutonniere deformities; **B)** and **C)**: Small sores and redness on anterior tibial region, and indolent cutaneous ulcer developed over the bony area of the elbow, both consistent with vasculitis; and **D)**: Residual shallow skin ulcer on the hospital discharge.

Discussion

RA is a very common inflammatory artropathy affecting 1-2% of population, mainly females [1]. Pulmonary changes associated with RA include necrobiotic nodules, Caplan syndrome, pleurisy, pleural effusion, diffuse interstitial disease, pulmonary arteritis and pulmonary hypertension [1-12]. This 65-year-old woman presented with RA, in addition to a right elbow ulcer and necrobiotic pulmonary nodules, which are extra-articular manifestations more often observed in males [3]. Subcutaneous nodules of RA are frequently found on areas under external pressure as forearms and elbows, and can evolve with necrosis giving origin to local cutaneous ulcers [1]. She presented cavitary pulmonary opacities with features strongly consistent with necrobiotic nodules [2, 10-12]; however, the presence of minute dust particulates could not be totally excluded in this study. Therefore, a main concern about the pulmonary nodules in this patient is the Caplan syndrome. Anthony Caplan (1953) first described the typical radiological features of massive pulmonary changes in 51 coal-miners (0.4%) with concomitant pneumoconiosis and RA [9]. The well-defined (0.5 to 5 cm) opacities appeared round to oval, predominantly in peripheral areas of both lungs [9]. Caplan believed that even minimal quantity of dust must be present to origin those changes; moreover, there were three fatal ca-

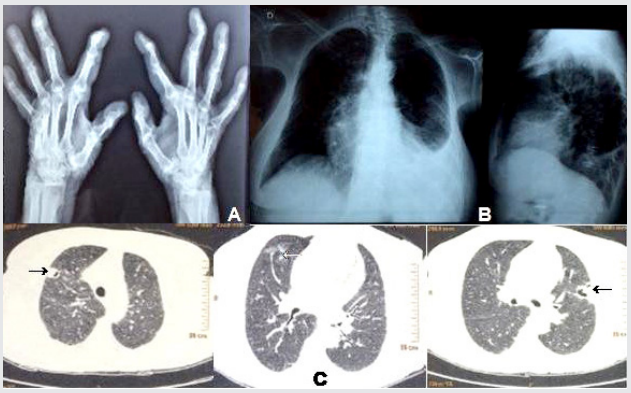

Figure 2. A) Typical radiographic osteoarticular changes of rheumatoid arthritis including periarticular osteoporosis and erosions, articular narrowings, and disruption in the carpus; **B)** Chest radiography showing residual images in the lung parenchyma, and left pleural effusion; and **C)** Computed tomography of thorax revealing opacities with ground-glass attenuation, and centrilobular nodules with tree-in-bud pattern, predominantly in the left upper lobe, in addition to multiple subpleural nodules presenting cavitations (arrows) in both pulmonary fields.

ses, all with images of pulmonary cavities, and respective necropsy studies revealed the diagnosis of tuberculosis in addition to RA and pneumoconiosis [9]. The patient of this case study denied occupational or accidental exposure to environmental dust, and the repeated search for pulmonary and cutaneous mycobacterial infections resulted negative. Notwithstanding, she underwent a course of treatment utilizing anti-tuberculosis medications; worthy of note, the imaging studies of control did not show significant reduction of the lesions.

Similar to the present case report, Gómez Herrero et al. (2012) described two tobacco smokers with microscopicic diagnosis of necrobiotic rheumatoid nodules in absence of pneumoconiosis [2]. Aghir et al. (2013) reported a 59-year-old man, heavy smoker with no kind of pneumoconiosis, who had elevated levels of rheumatoid factor and pulmonary nodules suspected of tuberculosis relapse [10]. He was treated with anti-tuberculosis second regimen, but the nodules evolved with cavitations; biopsy by thoracotomy revealed histopathology diagnosis of rheumatoid nodules [10]. Jolles et al. (1989) described pulmonary nodules in seven smokers with diagnosis of RA and positive rheumatoid factor; in two of the individuals, the nodules showed cavitation [11]. Lung malignancy was the etiology of nodules in all these cases; and the authors highlighted the role of tobacco smoking on the development of lung cancer, as well as of pulmonary nodules in RA [11]. Worthy on note in the present case study is the elevated level of anti-cyclic citrullinated peptide, which has been associated with extra-articular manifestations of RA, including lung nodules [4-6]. One must emphasize that the result of the test was 17 times over the upper limit of normal range. Studies have indicated that these antibodies can be specific for RA and play a physiopathologic role; they also may be related to the smoking-induced inflammatory process [4]; as could be with antrachosis that invariably follows chronic pulmonary changes observed in heavy smokers [10].

In conclusion, pulmonary rheumatoid nodules may precede osteoarticular manifestations in people with RA; thus, rheumatoid factor should be included in the routine investigation of pulmonary nodules. These nodules are associated with vasculitis of small vessels, which can cause cutaneous ulcers. Central necrosis of nodules causes cavitation, phenomenon that can mimic the imaging features presented by infectious and malignant nodules, posing additional challenges in this setting [11]. Case studies might contribute to further research about not entirely clear immune responses to citrullinated proteins involving pulmonary structures in patients with diagnosis of RA.

Conflicts of interest

The authors have no conflict of interest to disclose.

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Author contributions

The authors have the same contribution in the manuscript preparation.

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