Case report

Kartagener Syndrome and Rheumatoid Arthritis. Case Report

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Síndrome de Kartagener y artritis reumatoide. Reporte de caso

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Abstract
Case presentation. A 26-year-old woman, under follow-up by the rheumatology specialty since she was 17 years old, when she consulted with a history of one year of evolution of polyarticular disease of large and small joints, additive, symmetrical, accompanied by fatigue and morning stiffness for more than one hour. Positive rheumatoid factor was also reported. Additionally, the patient had a history of repeated sinobronchial processes since childhood. Medical examination revealed sinus pain in the paranasal sinuses, dextrocardia, and bronchiectasis, confirmed by imaging studies, which led to the diagnosis of Kartagener's syndrome. **Treatment.** The patient presented the severe clinical activity of rheumatoid arthritis. The treatment was started with methotrexate 10 mg orally one day a week, prednisone 5 mg a day, and folic acid 5 mg a week and periodic appointments, controlling the activity data and adverse effects of the drugs, with liver tests, hemogram, and transaminases. The pneumology department recommended the inclusion of the patient in a respiratory rehabilitation program as well as the use of azithromycin 500 mg every day for three days during periods of exacerbation. **Outcome.** The treatment was successful in maintaining a mild activity of the rheumatoid arthritis and without exacerbation of respiratory symptoms.

Keywords
Kartagener Syndrome, Dextrocardia, Ciliary Motility Disorders, Arthritis, Rheumatoid.

Resumen
Presentación del caso. Se trata de una mujer de 26 años de edad, en seguimiento por la especialidad de reumatología desde los 17 años, cuando consultó con historia de un año de evolución de síndrome poliarticular de grandes y pequeñas articulaciones, aditivo, simétrico acompañado de fatiga, rigidez matutina mayor de una hora. Se reportó además factor reumatoide positivo. La radiografía de ambas manos presentó erosiones, que confirmó el diagnóstico de artritis reumatoide. Adicionalmente, la paciente tenía el antecedente de procesos sinobronquiales a repetición desde su infancia. En la evaluación médica se identificó dolor en los senos paranasales, dextrocardia y bronquiectasias, confirmados por los estudios de imágenes, que permitió concluir en el diagnóstico de síndrome de Kartagener. **Intervención terapéutica.** La paciente presentaba actividad clínica severa de la artritis reumatoide, se inició el tratamiento con metotrexato 10 mg vía oral un día a la semana, prednisona 5 mg al día y ácido fólico 5 mg a la semana y citas periódicas, controlando los datos de actividad y efectos adversos de los medicamentos, con pruebas hepáticas, hemograma y transaminasas. La especialidad de neumología recomendó la inclusión de la paciente en un programa de rehabilitación respiratoria, así como el uso de azitromicina 500 mg cada día por tres días en los períodos de agudización. **Evolución clínica.** El tratamiento logró mantener una actividad leve de la artritis reumatoide y sin exacerbación de los síntomas respiratorios.

Palabras clave
Síndrome de Kartagener, Dextrocardia, Discinesia Ciliar Primaria, Artritis Reumatoide.

Introduction

Kartagener syndrome (KS) is an autosomal recessive disorder consisting of the triad of sinusitis, bronchiectasis and *situs inversus* with dextrocardia and represents a subgroup of primary ciliary dyskinesia (PCD). It is a genetically heterogeneous respiratory disorder characterized by chronic upper and lower respiratory tract disease.[1,2] The estimated worldwide prevalence is 1/15 000 to 1/30 000 live births[1].

Approximately 50 % of patients with SCD have laterality defects (including *situs inversus totalis* and, less frequently, heterotaxy and congenital heart disease), reflecting dysfunction of embryologic nodal cilia.[1-3]

Most mutations identified as causes of PCD involve the heavy (DNAH5) or intermediate (DNAI3) mutation, which chains dynein genes in the ciliary outer dynein arms, although some mutations in other genes have been observed. Clinical molecular genetic testing is available for the most common mutations.[4,5] Ciliary ultrastructural analysis reveals defective dynein arms in more than 80 % of patients, although defects in other axonemal components have also been observed.[6,7]

The respiratory manifestations of PCD are chronic bronchitis, bronchiectasis, chronic rhinosinusitis, chronic otitis media, and less frequently infertility and are the result of impaired mucociliary clearance due to a defective axoneme structure.[6,7] Cases of KS with glomerular alterations and neoplasms[8] and rheumatoid arthritis (RA) have been reported. Several theories have been proposed on pathogenesis, one of them accepts that environmental factors such as smoking, repeated infections and periodontitis play an important role in the development of the disease in a genetically susceptible person.[9]

Case presentation

The patient is a 26-year-old, nulliparous woman with no family history of autoimmune diseases who has been under follow-up by the rheumatology specialty since she was 17 years old due to mild to moderate intensity joint pain in the wrist, metacarpophalangeal, proximal interphalangeal, elbow and knee joints, of one year of evolution, which presented with greater intensity in the mornings and improved with exercise, accompanied by systemic manifestations, including unquantified weight loss, morning stiffness lasting more than one hour and fatigue when carrying out her activities; she had received treatment with non-steroidal anti-inflammatory drugs that did not generate clinical improvement.

During a routine examination, the patient was diagnosed with sinobronchial syndrome, characterized by frequent crises since she was two years old, which had been treated with antibiotics and expectorants. On physical evaluation, the patient was found to be thin, tachycardic, with a nasal voice, pain on palpation of the maxillary regions, expiratory wheezing, and palpable liver 2 cm below the left costal ridge. In addition, she had synovial hypertrophy in the elbows, wrists, metacarpophalangeal and proximal interphalangeal joints with swan neck deformity (Figure 1 and 2), flexion contracture at 30 degrees, and nodules in the right elbow. She also had a heart rate of 109 bpm, respiratory rate of 18 rpm, ambient air oxygen saturation of 97 % of 81 pounds, height of 1.50 m, and a body mass index of 16.4 kg/m^2.

Laboratory tests and imaging studies reported moderate anemia with elevated erythrocyte sedimentation rate and rheumatoid factor (RF) (Table 1).

Treatment

Due to the detection of a moderate clinical index of disease activity, she was given outpatient treatment with methotrexate 7.5 mg and folic acid 5 mg weekly, prednisone 5 mg and calcium carbonate 1200 mg daily. This treatment was based on the recommendations of the American College of Rheumatology guidelines for patients with RA.[10]

After two months, she was evaluated by rheumatology, where a slight improvement in hemoglobin was identified, and she presented with mild leukocytosis (Table 1).

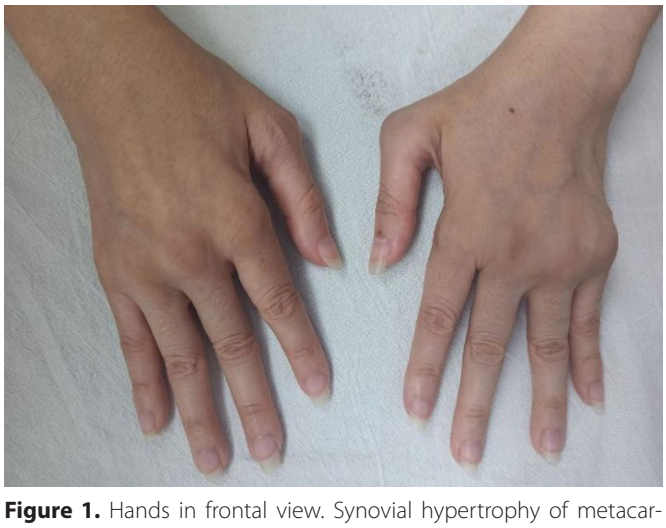

Figure 1. Hands in frontal view. Synovial hypertrophy of metacarpophalangeal joints, proximal, ulnar deviation

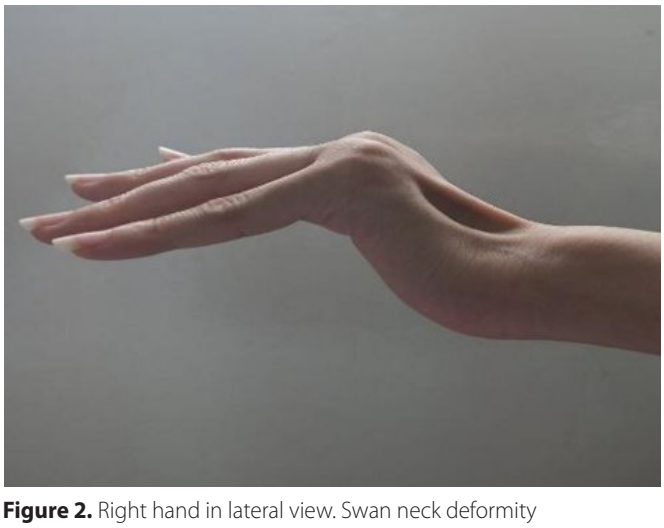

Figure 2. Right hand in lateral view. Swan neck deformity

Posteroanterior chest X-ray reported dextrocardia, with a gastric bubble displaced to the right and bilateral basal bronchial dilatations (Figure 3).

Sinus radiography identified opacity of the frontal and maxillary sinuses, which confirmed the diagnosis of chronic sinusitis. At the same time, posteroanterior radiography of both hands reported soft tissue enlargement with joint space narrowing in the proximal interphalangeal areas, metacarpophalangeal, carpal, and radiocarpal joints, and juxta-articular osteopenia and erosions, which led to the diagnosis of erosive rheumatoid arthritis radiological grade III.

The echocardiogram described the left atrium within normal diameters and the left ventricle with preserved thickness, diameters, and systolic function (left ventricular ejection fraction: 66 %) with normal right cavities and dextrocardia. Computed tomography also reported dextrocardia and multiple moderate-caliber basal bronchiectasis (Figure 4 and 5).

After four months, no adverse effects to methotrexate were identified, and she continued with moderate activity, so the dose of methotrexate was increased to 12.5 mg every week without changes in the prednisone, folic acid, and calcium carbonate.

The pneumology department recommended the inclusion of the patient in a respiratory rehabilitation program, along with the administration of azithromycin 500 mg daily for three days during periods of exacerbation.

Clinical evolution

After six months of treatment, a mild activity of rheumatoid arthritis was identified. Therefore, it was indicated to continue the treatment and periodic specialty follow-up.

Table 1. Laboratory tests

Examination performed	Medical Follow-up 1	Medical Follow-up 2
Hemoglobin	9.4 gr/dL	11.0 gr %
Hematocrit	31.4 %	-
White blood cells	7000 mm^3	11 700/mm^3
Lymphocytes	26.3 %	-
Neutrophils	65 %	-
Monocytes	9 %	-
Platelets	323 000 mm^3	-
Erythrocyte sedimentation rate	56 mm/h	-
Rheumatoid factor	128 UI/mL	-
Total proteins	8.3 gr %	-
Albumin	3.9 gr %	-
Globulin	4.4 gr %	-
Aspartate aminotransferase (AST)	12 UI/mL	30 UI/l.
Alanine aminotransferase (ALT)	9 UI/mL	28 UI/l
Serum creatinine	-	0.8 mg %

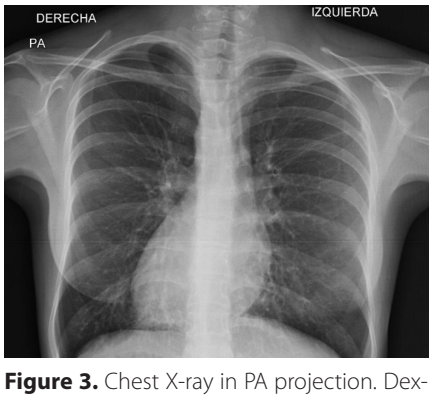

Figure 3. Chest X-ray in PA projection. Dextrocardia, parahilar dlation with parahilar and basal bronchiectasis

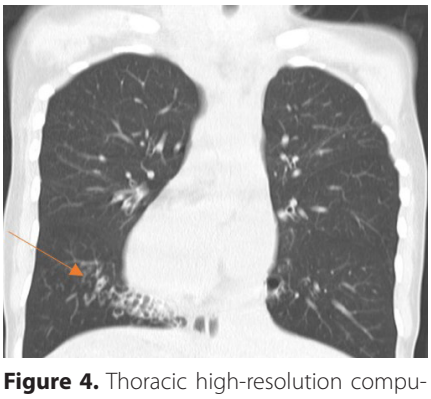

Figure 4. Thoracic high-resolution computed tomography, sagittal section. Cylindrical bronchial and tram-track bronchiectasis (indicated with arrow)

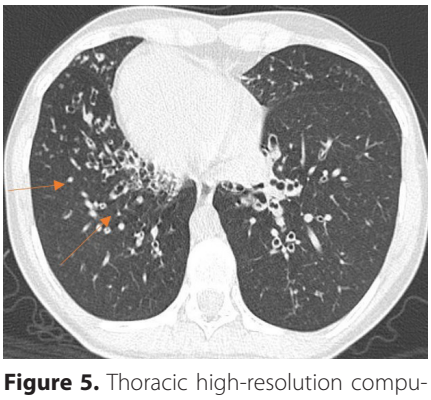

Figure 5. Thoracic high-resolution computed tomography, coronal section. Dextrocardia, multiple basal bronchiectasis of moderate caliber (indicated with arrows)

Clinical diagnosis

The diagnoses of sinusitis, dextrocardia, and bronchiectasis that constitute the triad of Kartagener's syndrome were integrated. Likewise, in this case, it was associated with rheumatoid arthritis due to the additive and symmetrical involvement of more than four joints, elevated erythrocyte sedimentation, positive rheumatoid factor at high titers, and the presence of erosions in hand radiographs.

Discussion

The diagnosis of KS is based on clinical features of persistent wet cough, *situs* abnormalities, congenital heart defects, persistent rhinitis, chronic otitis media with or without hearing loss, history in term newborns of neonatal upper and lower respiratory symptoms or neonatal intensive care.[3] Diagnostic methods include transmission electron microscopy that identifies specific ciliary ultrastructural defects in biopsy specimens and high-speed video microscopy to evaluate cilia waveform and beat frequency. Another method is the study through diagnostic immunofluorescence microscopy and electron microscopy, which helps to identify individual defects of the ciliary structure. Molecular genetic testing of the causative genes can confirm the diagnosis. Currently, 33 mutations in more than 40 genes associated with PCD have been identified.[4-6]

The characteristic clinical findings of CPD are repeated bronchial processes since infancy, and the radiological findings are chronic sinusitis, dextrocardia, left liver, and bronchiectasis, characteristic of KS.[2,3] This case highlights the importance of timely diagnosis of CPD in patients with chronic respiratory tract infections since birth or infancy, and ideally, early diagnosis to prescribe timely treatment, thus avoiding permanent sequelae such as chronic sinusitis and bronchiectasis.

On the other hand, the diagnosis of RA was confirmed by clinical analysis, additive symmetrical involvement of large and small joints, and the detection of erythrocyte sedimentation disturbances, positive rheumatoid factor, and the presence of erosions on radiographic images.[11]

Treatment is on measures to prevent the frequency and severity of respiratory infections. Aggressive treatment to improve mucus clearance, such as physical therapy and inhalation therapy, as well as intranasal steroids and nasal lavage are recommended as a treatment for sinusitis.[4,5,7]

The presentation of KS and RA is rare and there is no evidence available to support a causal relationship between both diseases. Some cases have been reported, including an 11-year-old adolescent with a diagnosis of juvenile idiopathic arthritis and negative RF, who evolved with good response after treatment with methotrexate and prednisone; a 60-year-old woman, diabetic and hypertensive, with non-erosive RA, positive RF, who was in remission due to this received chloroquine phosphate and methylprednisolone; a 38-year-old woman with positive RF, erosive, treated with prednisone 7.5 mg daily and methotrexate 15 mg once a week; a 35-year-old man with positive RF due to erosive arthritis who had a good evolution with prednisone 10 mg daily and methotrexate 15 mg every week; finally, an 18-year-old adolescent with RA, non-erosive and negative RF, who received methotrexate at 20 mg/ once a week and prednisone 5 mg daily.[9,12,13]

Certain environmental factors are considered to play an important role in the development of RA in genetically susceptible individuals. Among them, repeated infections and periodontitis are mentioned, two factors that were found to be present in the patient.[11,14,15] Increasing evidence suggests that autoimmunity in RA patients is initiated outside the joint. This theory is supported by the observation that circulating autoantibodies, including RF and anti-citrullinated protein antibodies, can be detected in many subjects years before the development of initial joint symptoms, leading to a diagnosis of RA. Of the possible extra-articular sites implicated in disease onset, mucosal tissues have captured increasing attention. Several lines of research have separately implicated mucosal tissues from different anatomical locations as possible sites of RA onset, including those of the lung and oral cavity.[16,18]

One of the main bacteria implicated in the development of periodontal disease is Porphyromonas gingivalis. Gingival tissue affected by periodontitis has been shown to trigger a citrulline-specific autoimmune response characterized by an antibody response to citrullinated proteins, accelerated by increased expression of neutrophil extracellular traps.

These citrullinated proteins and their related antibodies have been detected in the blood and joints of RA patients, as well as in the inflamed gingiva of patients with periodontitis.[19,20]

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