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SCIENTIFIC LETTER

Interstitial lung disease associated with systemic-onset juvenile idiopathic arthritis

Enfermedad pulmonar intersticial asociada a artritis idiopática juvenil de inicio sistémico

Dear Editor:

Systemic juvenile idiopathic arthritis (sJIA), also known as pediatric-onset Still disease, is an autoinflammatory disorder that affects children aged less than 16 years and manifests with fever, arthritis, rashes, polyserositis, organomegaly, and/or lymph node enlargement in association with leukocytosis and elevation of acute-phase reactants. It accounts for 10%–20% of cases of JIA.[1]

Macrophage activation syndrome (MAS) and sJIA-associated interstitial lung disease (sJIA-ILD) are among its most significant complications. The latter has a silent course with progressive development of cough, desaturation, digital clubbing, and abnormalities in lung function tests. However, high-resolution computed tomography (HRCT) can detect changes from onset.

Systemic JIA is an infrequent cause of pediatric interstitial lung disease, yet a very serious one, as it tends to affect young children and go undetected, resulting in significant morbidity and mortality. We present the cases of two patients with sJIA-ILD managed in our hospital that illustrate how early detection and treatment improve disease outcomes.[2]

The first is a girl aged 3.5 years, who is HLA DRB1*15-positive and had no history of interest at the time of diagnosis of sJIA at 13 months, with a favorable response to initial treatment with IV methylprednisolone and IL-1 blocking with anakinra. During the follow-up, she experienced mild relapses that responded to reintroduction of prednisone; and was readmitted at 25 months for refractory MAS that required combination therapy with ruxolitinib and emapalumab. At the time of admission, she had a mild unproductive cough in absence of dyspnea and did not need oxygen therapy. The patient underwent a HRCT scan that revealed severe diffuse bilateral lung involvement and was treated with canakinumab, ruxolitinib, and tacrolimus. The follow-up HRCT scan at one year showed complete resolution (Fig. 1).

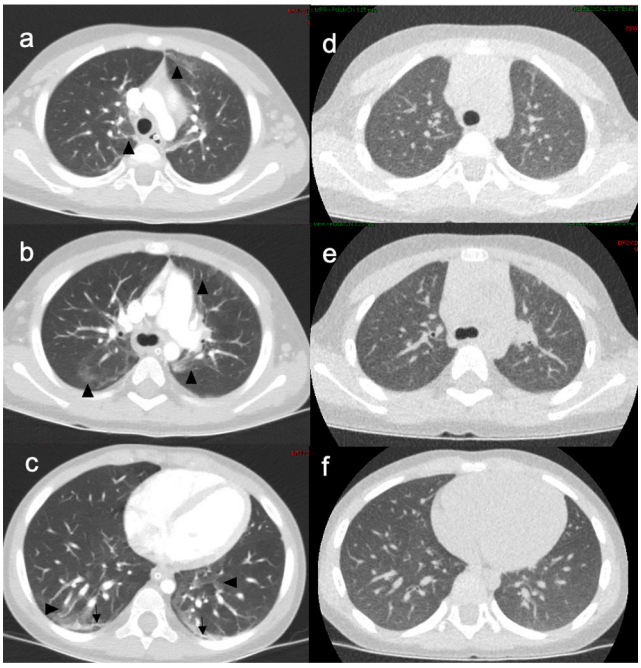

Figure 1 (a–c): initial contrast-enhanced CT scan, with acquisition of images in full inspiration with the patient under sedation and ventilated via a laryngeal mask. Perihilar and peripheral areas of ground-glass opacity (arrowheads). Peripheral linear bands in the lower lobes (black arrows). (d–f): Follow-up CT scan after treatment (acquired during spontaneous breathing without intravenous contrast). Complete radiological resolution, with no residual lesions. Resolution of parenchymal involvement.

The other patient is a boy aged 3.5 years, HLA DRB1*15-positive, with trisomy 21 and a ventricular septal defect, who received the diagnosis of sJIA at age 16 months and responded to initial treatment with IV methylprednisolone and methotrexate. As prednisone was tapered off, the patient experienced a severe polyarticular relapse that responded to tofacitinib monotherapy. The patient was lost to follow-up, and treatment was discontinued before the closure of the ventricular septal defect. Five months later, he experienced a new relapse of arthritis, which was controlled with prednisone and anakinra. Although the patient had no respiratory symptoms, a combination of risk factors

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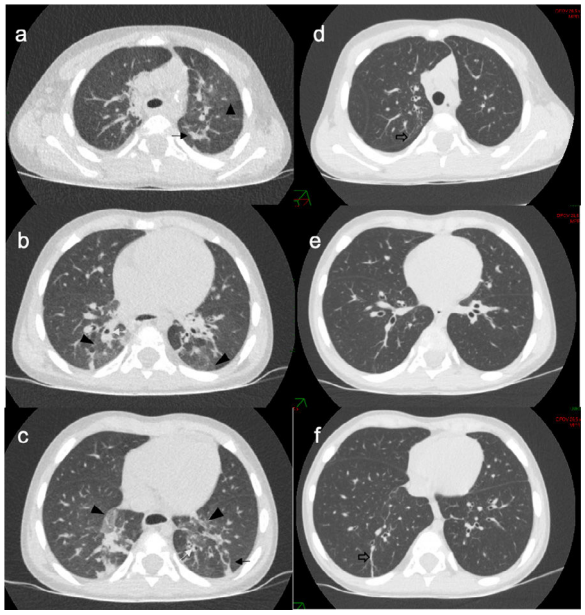

Figure 2 (a–c): initial chest CT showing diffuse ground-glass opacities with a central/perihilar distribution, predominantly in the lower lobes, and peripheral involvement of the anterior and apicoposterior segments of the left upper lobe. Patchy peripheral linear atelectasis and bibasilar peribronchovascular thickening are also present. (d–f) Follow-up chest CT after treatment showing resolution of the ground-glass opacities, peribronchovascular thickening, and peripheral atelectasis. Residual parenchymal bands persist in the right upper and lower lobes (hollow arrows).

prompted performance of an HRCT scan of the chest that revealed diffuse ground-glass opacity with bronchial thickening, which was treated with a combination of tacrolimus and anakinra. The follow-up HRCT scan of the chest at one year showed radiological resolution (Fig. 2).

The pulmonary complications associated with JIA were not known until 2013, when the first cohort study of patients with pulmonary involvement was published; since then, other studies have further characterized this complication.[3]

The risk factors for developing sJIA-ILD include a younger age at onset, recurrent or refractory MAS, HLA DRB1*15 carriage, and trisomy 21.

Carriage of certain HLA alleles, and of HLA DRB1*15 in particular, appears to be associated with an increased frequency of drug reactions with eosinophilia and systemic symptoms (DRESS) to drugs used in the management of sJIA, and more recent studies have reported that this allele is overrepresented in patients with the disease. Since sJIA-ILD had not been described prior to the use of biologic agents, it has been hypothesized that there may be an association between the use of IL-1/IL-6 inhibitors, this allele, and eosinophilia, which is detectable even before treatment initiation.[4] The evidence remains limited, and no clear causal relationship has been established; therefore, clinical practice guidelines do not recommend delaying biologic therapy in patients with sJIA solely based on the risk of developing sJIA-ILD.[5]

Given the young age of most patients, which precludes performance of lung function tests, and the absence of specific symptoms until more advanced stages, HRCT remains the gold standard for diagnosing sJIA-ILD. There is no specific radiologic pattern associated with this condition; usually, there are areas of ground glass opacity associated with septal or peribronchovascular thickening, similar to the findings described in the context of pulmonary alveolar proteinosis, and other possible findings include a tree-in-bud pattern, peripheral consolidation, and lymphadenopathy.[2]

Several immunosuppressants used to treat interstitial lung disease in other rheumatic conditions, such as tacrolimus or mycophenolate, have been used in sJIA-ILD, but the evidence on the subject is limited. In the absence of standardized guidelines, JAK-STAT pathway inhibitors, such as tofacitinib or ruxolitinib, are a promising alternative.[2]

Although rare, MAS and sJIA-ILD (which occur in 20% and 10% of cases, respectively) are serious life-threatening complications; in the case of sJIA-ILD, the mortality can be as high as 68%.[6] Since early initiation of treatment is essential for improving outcomes and requires a high index of suspicion, a multidisciplinary approach, and prompt performance of HRCT, these patients should be evaluated at referral hospitals.

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