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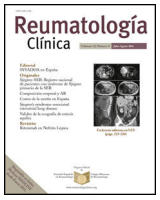

Case Report

Crohn's disease in a patient with systemic onset juvenile idiopathic arthritis. Association or associated side effect of treatment?☆

Laura Martín Pedraz,[a,*] Rocío Galindo Zavala,[a] Javier Blasco Alonso,[b] Víctor Manuel Navas López,[b] Esmeralda Núñez Cuadros[a]

[a] *Sección de Reumatología Pediátrica, UGC Pediatría, Hospital Regional Universitario de Málaga, Málaga, Spain*
[b] *Sección de Gastroenterología y Nutrición Infantil, UGC Pediatría, Hospital Regional Universitario de Málaga, Málaga, Spain*

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ABSTRACT

The progression of systemic-onset juvenile idiopathic arthritis (JIAs) to the different forms of presentation of inflammatory bowel disease is extremely rare. We present the first report of a patient with SJIA that progressed to Crohn's disease in which mutations have been detected in genes responsible for the adequate regulation of the innate immune system.

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Enfermedad de Crohn en paciente con artritis idiopática juvenil de inicio sistémico: ¿asociación o complicación asociada al tratamiento?

Palabras clave:
Enfermedad de Crohn
Artritis idiopática juvenil de inicio sistémico
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RESUMEN

La evolución de la artritis idiopática juvenil de inicio sistémico (AIJs) hacia las diferentes formas de presentación de enfermedad inflamatoria intestinal es extremadamente infrecuente. Presentamos la que, hasta ahora, es la primera comunicación de un paciente con AIJs con evolución a enfermedad de Crohn en el que se han detectado mutaciones en genes responsables de la adecuada regulación del sistema inmune innato.

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Introduction

Patients with juvenile idiopathic arthritis (JIA) are at increased risk for developing inflammatory bowel disease (IBD)[1], although their association with systemic-onset JIAs is exceptional[2–4], Mutations in genes causing immune deficiency due to immune dysregulation, common to both entities[5], or the role of anti-IL1 treatments are hypothesised[2,3].

Clinical case report

We present the case of an 8-year old girl with fever of one month's duration, anorexia, sweating, and weight loss. Physical examination revealed no abnormalities.

Laboratory tests revealed leukocytosis (25,000/mm^3) with a shift to the left, thrombocytosis (528,000/mm^3), CRP 163 mg/l, ESR 92 mm, ferritin 737 ng/mL, and hypergammaglobulinaemia (IgG 2,650 mg/dl). The rest of the biochemical study failed to exhibit any further alterations. The infectious screening, which included tuberculosis, was negative. ANA and rheumatoid factor were similarly negative. Faecal calprotectin (FC) was 58 ng/g. Chest X-ray, abdominal ultrasound, thoracoabdominal CT, echocardiography, MRI, and bone scan displayed no pathological findings. The fundus examination was normal and the bone marrow biopsy exhibited no abnormalities.

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* Corresponding author.
E-mail address: pedraz88@hotmail.com (L. Martín Pedraz).

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Table 1
Paediatric series of JIAs with subsequent development of IBD.

Sample size	Maller et al.[3], 2020 n = 16	*Hügle B* et al.[2], 2017 *n = 3*	Van Dijken et al.[4], 2011 n = 2
Sex (male)	50.0%	66.7%	–
Mean age at diagnosis of JIAs	9.9 years (range 1.5-16.1 years)	12.5 years (range 6.8-15.8 years)	9.5 years (range 5-14 years)
Most common clinical manifestations at the onset of JIAs	Arthritis 100% Fever 94% Exanthema 69%	Arthritis 100% Fever 100% Exanthema 100%	–
Mean time of evolution of JIA at the time of IBD diagnosis	3 years (range 1.5-9 years)	3.3 years (range 0.9-4.7 years)	8.7 years (range 5.2-12.3 years)
Most common clinical manifestations at the onset of IBD	Diarrhoea 75% Abdominal pain 69% Weight loss 63%	Diarrhoea 100% Hematochezia 33.3%	–
IBD subtype	CD 81% Undetermined colitis 19%	CD 66.7% Colitis ulcerosa 33.3%	CD 100%
Type of biological treatment prior to onset of IBD	Anti IL-1 (anakinra or canakinumab) 50% Anti TNF-α (etanercept) 31% Anti IL-6 (tocilizumab) 12.5%	Anti IL-1 100% Anakinra 66.7% Canakinumab 33.3%	Anti TNF-α (etanercept) 100%
Mean time since biological treatment initiation to onset of IBD	–	2.5 years (range 0.9-4.4 years)	1.6 years (range .3-3.0 years)
Type of biological treatment following onset of IBD	Anti TNF-α (adalimumab or infliximab) 75% Anti-IL1 6% Anti IL-6 (tocilizumab) 6%	Anti TNF-α (infliximab) 66.7% Anti IL-1 (anakinra) 33.3%	Anti TNF-α (infliximab) 50%
Evolution following onset of IBD (% inactive disease)	JIAs: 77% IBD: 23%	JIAs: 100% EII: 66.7%	IBD: 100%

CD: Crohn's disease; IBD: Inflammatory bowel disease; JIAs: Systemic-onset juvenile idiopathic arthritis.

After one week she developed right axillary adenopathy, hypoechoic on ultrasound, and with pathological uptake on the PET-CT scan. After surgical excision, the anatomopathological and microbiological study showed no alterations. Subsequently, he developed swelling and limitation of the left knee, with joint effusion with no synovial hypertrophy.

With a diagnosis of JIA (ILAR 2001 criteria), oral prednisone (1.5 mg/ kg/ day) was started, to which subcutaneous anakinra (2 mg/ kg/ day) had to added after 3 weeks, due to relapse after decreasing the corticosteroids. One month later, it was substituted for subcutaneous canakinumab (4 mg/ kg/ 4weeks), making it possible to administer doses every 6 weeks, without incident, and she remained asymptomatic for 3 years.

After this, the patient once again began to have fever, arthralgias, and an increase in CRP. Given her incomplete clinical and analytical response to oral prednisone (1 mg/ kg/ day), intravenous tocilizumab (8 mg/ kg/ 2 weeks) was initiated, with partial improvement.

One month later she was readmitted for abdominal pain and haematochezia. Laboratory tests yielded haemoglobin values of 7.6 g/ dl and CF 3132 ug/ g. After ultrasound evidence of ileocolitis, upper and lower gastrointestinal endoscopy was performed and a diagnosis of Crohn's disease (CD) was established according to the Oporto criteria[6] and the Paris classification[7]. The genetic panel for autoinflammatory diseases resulted in a probably benign mutation (pR702W) and a mutation of uncertain significance (p1007finsC), both in heterozygosis, of the NOD2 gene.

Tocilizumab was discontinued, and subcutaneous adalimumab (160-80-40 mg/ 2 weeks) and oral prednisone (1.5 mg/ kg/ day) were started, requiring combo therapy with azathioprine. She is currently asymptomatic on adalimumab monotherapy, with CF < 15.6 ug/ g.

Discussion

IBD very rarely develops as an extra-articular manifestation of JIA[2–4]. Although some authors propose that pharmacological blockade of IL-1 would favour the phenotypic change of JIA to IBD[2,3], this evolution has also been detected in individuals with other treatments (Table 1)[3,4] in whom this hypothesis is not supported.

The JIA-IBD overlap is an alternative to be considered, with good response to treatment based on anti-TNF drugs and even disappearance of systemic symptoms in patients with JIA who subsequently progress to CD[3]. The description of mutations of the LACC1 gene, associated with both entities, would support this possibility[5].

The detection of mutations in the NOD2 gene associated with CD in our patient poses the alternative that the initial symptoms, compatible with JIAs, were the set of extraintestinal manifestations of the onset of an underlying CD, although the normal CF and imaging tests allowed this diagnosis to be ruled out. We do not know the role that anti-IL1 treatment played in lengthening the latency period until the development of classic CD symptoms[8].

Conclusions

As this is a single case, and given the absence of genetic studies in the published series[2–4], it is not possible to extrapolate conclusions, and further studies are needed to prove or disprove these hypotheses. Be that as it may, in diseases with a diagnosis of exclusion, such as JIA, other diagnostic alternatives or the association with other diseases due to immune dysregulation should be assessed in the event of the appearance of atypical manifestations or loss of effectiveness of the usual treatment.

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Conflict of interests

None.

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