

ASSOCIATION OF SYSTEMIC-ONSET  
JUVENILE IDIOPATHIC ARTHRITIS AND  
CELIAC DISEASE – A CASE REPORT

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### Abstract

**Introduction:** In a 28-year period, 5,508 patients were followed at our Paediatric Rheumatology Division and 712 (13%) patients had juvenile idiopathic arthritis (JIA) (ILAR criteria). One (0.14%) of them had association with celiac disease (CD), with predominance of gastrointestinal manifestations and this case was described herein.

**Case report:** A 10-years-old female patient was hospitalized with persistent fever, weight loss, asthenia, anorexia and an evanescent pink macular rash. After one week, she presented arthritis of left knee and ankle with duration of 75 days. The initial laboratory exams revealed anemia and elevation of inflammatory markers. Immunological tests were positive for anti-endomysial antibodies IgA and anti-thyroglobulin antibody. The diagnosis of systemic JIA was established and indomethacin (2.0 mg/kg/day) was started with improvement of arthritis. The patient evolved with vomiting, diarrhea and abdominal pain and upper gastrointestinal barium study showed areas of small bowel dilatation and thickening of folds, suggestive of malabsorption syndrome. Colonoscopy was normal and small intestinal biopsy was compatible with CD.

**Discussion:** We reported a case of a rare association of early diagnosis of systemic JIA occurring simultaneously with CD. This study reinforces the importance of taking into account the possible association of organ-specific autoimmune diseases during JIA course.

**Keywords:** Systemic Onset Juvenile Idiopathic Arthritis; Celiac Disease; Children.

### Introduction

Systemic-onset juvenile idiopathic arthritis (SoJIA) is a chronic inflammatory disease of unknown etiology characterized by chronic arthritis, fever and often associated with other signs and symptoms, such as: skin rash, hepatosplenomegaly, pleuritis and pericarditis<sup>1,2</sup>. Eventually these patients may also present gastrointestinal involvement, such as abdominal pain and mesenteric lymphadenopathy<sup>2</sup>.

Of note, celiac disease (CD) is an autoimmune enteropathy illness characterized by the presence of at least four of the following criteria: clinical manifestations (diarrhea, stunting and/or iron deficiency anemia), presence of celiac disease IgA class antibodies, HLA-DQ2 or DQ8 genotype, small intestine biopsy compatible with celiac enteropathy, and response to gluten-free diet<sup>3</sup>.

Arthritis, involving both the peripheral and axial skeletal, might be an early extra-intestinal manifestations of CD<sup>4</sup>. Additionally, CD has also been rarely described in patients with chronic arthritis, such as JIA, mainly in oligoarticular and polyarticular subtypes<sup>5,6</sup>. To our information, only two cases of CD were reported in SoJIA patients during follow-up of disease<sup>5,7</sup>.

From January 1983 to December 2010, 5,508 patients were followed at the Paediatric Rheumatology Unit of Instituto da Criança da Faculdade de Medicina da Universidade de São Paulo and 712 (13%) patients fulfilled the International League of Associations for Rheumatism (ILAR) classification criteria for JIA<sup>1</sup>. One of these (0.14%) patients had a concomitant diagnosis of SoJIA and CD, and this case was described herein.

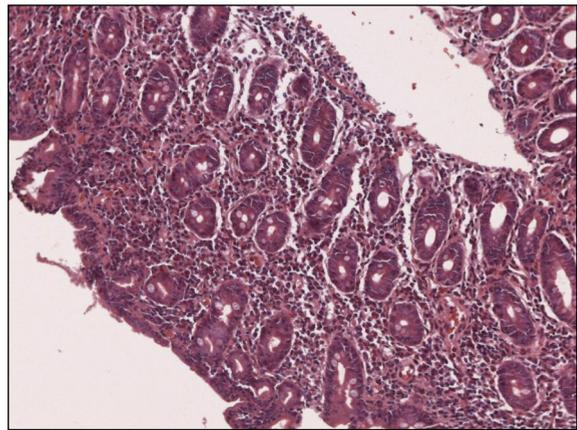
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## Case Report

A 10-years-old female patient was hospitalized in our University Hospital with persistent high fever (39-40°C) for 25 consecutive days associated with an evanescent erythematous rash, weight loss (9 kg in 25 days), asthenia and anorexia. No epidemiology for Lyme disease, brucellosis and tuberculosis was reported. After one week of hospitalization, she presented hepatomegaly, chronic arthritis of left knee and ankle for a period of 75 days. The initial laboratory exams revealed hemoglobin 9.3 g/dL, hematocrit 28.5%, white blood cell count 6,700/mm<sup>3</sup> (73% neutrophils, 18% lymphocytes, 2% eosinophils and 7% monocyte), platelet count 492,000/mm<sup>3</sup>, thyroid stimulating hormone (TSH) 1.82 µU/mL (normal range 0.6-5.4 µU/mL) and free thyroxine 1.36 ng/dL (normal range 0.7-1.5 ng/dL). Erythrocyte sedimentation rate was 61 mm/1<sup>st</sup> hour and C-reactive protein 121 mg/L (normal < 5). She had normal cardiac examination according to pediatric cardiologist evaluation. The thoracic radiography and echocardiography were normal. The bone marrow aspiration was normal. Serologic tests, such as: hepatitis virus A, hepatitis virus B, hepatitis virus C, Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), toxoplasmosis and rubella, were all negative. Antistreptolysin o (ASLO) titer was 132 UI/mL and immunological tests were negative for the following serum antibodies: antinuclear antibody (ANA), anti-double-stranded DNA (anti-ds DNA), anti-Sm, anti-Ro, anti-La and anti-peroxidase (anti-TPO). Serum IgG was 1735 mg/dL (normal range 970-1710 mg/dL), IgM was 141 mg/dL (normal range 53-145 mg/dL) and IgA was 56 mg/dL (normal range 45-234 mg/dL). Therefore, the diagnosis of SoJIA was established according to the ILAR classification criteria<sup>1</sup> and indomethacin (2.0 mg/kg/day) was introduced with improvement of chronic arthritis after hospitalization, with persistence of fever, rash and hepatomegaly. At 10 years and 3 months of age, she presented vomiting, diarrhea and severe abdominal pain that worsened after food ingestion, and was re-admitted. At that hospitalization, upper gastrointestinal barium study showed small bowel dilatation and thickening of folds, suggestive of malabsorption syndrome. Abdominal ultrasound was normal. The abdominal computed tomography scan evidenced mild distension of small bowel. Upper endoscopy and colonoscopy were normal. Im-



**Figure 1.** Endoscopic biopsy of jejunum showed dense cellular infiltrate in the lamina propria, villous atrophy, crypt hyperplasia and elevated intraepithelial lymphocytes (IELs), compatible with celiac disease.

munoglobulin A (IgA) class anti-endomysial antibody (IgA-EMA) by indirect immunofluorescence was 1/40 (normal < 1/10). Remarkably, the endoscopic small bowel biopsy showed chronic duodenitis and jejunitis with dense cellular infiltrate in the lamina propria, villous atrophy, crypt hyperplasia and elevated intraepithelial lymphocytes (IELs), compatible with CD (Figure 1). A gluten-free diet was introduced with improvement of diarrhea, and the CD diagnosis was established<sup>3</sup>. In order to ensure the adherence to a complete removal of gluten from the diet, the patient remained hospitalized, however 29 days after CD diagnosis the patient evolved with sepsis by *Serratia sp* and died of septic shock.

## Discussion

We described a case of concomitant diagnosis of these two autoimmune diseases (SoJIA and CD) with a fatal outcome. These diagnoses were rarely observed in a large tertiary of pediatric hospital in Brazil.

CD is an immunologically based enteropathy characterized by sensitivity to gluten in genetically predisposed subjects<sup>3,5</sup>. Notably, similar mechanisms elicited by environmental triggers may induce the concomitant occurrence of multiple organ-specific autoimmune diseases in CD patients, such as type I diabetes mellitus, Graves' disease and Hashimoto's thyroiditis<sup>6,8</sup>.

Likewise, systemic autoimmune diseases, such

as JIA, may also be associated with this autoimmune enteropathy<sup>5-10</sup>. In fact, CD was previously reported in 2.5% to 6.5% of JIA children<sup>5,7,11,12</sup>. Of note, the most frequent JIA subtypes associated with CD were oligoarticular and polyarticular<sup>5,6</sup> and very rarely patients had SoJIA<sup>5</sup>. Notably, our patient presented classical features of SoJIA, including diary high fever during more than 2 weeks, chronic arthritis, evanescent rheumatoid rash and hepatomegaly together with the general symptoms, such as anorexia and weight loss, that in few months would evolve to typical gastrointestinal symptoms of CD. Differently to the present report, Alpigiani *et al.* had demonstrated CD diagnosis 3.5 and 4.6 years after JIA onset<sup>11</sup>, however the subtypes of these patients were not described.

Remarkably, CD frequently remains asymptomatic for years but may be associated with an increased risk of a second autoimmune disease<sup>5</sup>. Of note, the CD diagnosis requires at least four of the following criteria: presence of typical symptoms of celiac disease, positivity of serum celiac disease autoantibodies (IgA-EMA and/or anti-tissue transglutaminase) at high titer, HLA-DQ2 or DQ8 genotypes, celiac enteropathy at the small intestinal biopsy and response to the GFD<sup>3</sup>, as identified in our present case.

Differential diagnosis must be done with a variety of infections affecting small bowel mucosa. Furthermore, autoimmune enteropathy, secondary to the production of autoantibodies against enterocytes, is usually characterized by histologic findings of villous flattening and crypt hyperplasia, similarly to CD. Crohn disease may also be excluded, once it affects the upper gastrointestinal tract in up to 30% to 50% of cases. In addition, primary immunodeficiencies, such as common variable immunodeficiency, may be associated with autoimmune diseases such as JIA and CD<sup>13</sup>. Of note, the patient reported herein died of septic shock by *Serratia* sp. infection and presented lymphopenia lower than 1500 cells/uL, however Immunophenotyping of lymphocytes were not performed.

Our patient was prone to intestinal mucosal lesion associated to CD. In fact, *Serratia* bacteremia originates mainly from bloodstream, respiratory, gastrointestinal and urinary tract. Previous studies demonstrated hospital-acquired septic shock by *Serratia* in 14.8% and mortality rates related to *Serratia* bacteremia of 25% to 58%<sup>14</sup>.

CD treatment is based on a gluten-free diet, which can reduce articular and intestinal mani-

festations<sup>5,6,11</sup>. To our knowledge, the use of non-steroidal anti-inflammatory drugs, such as indomethacin, has no influence to the course of CD, as observed in our case.

In conclusion, we reported a case of early diagnosis of SoJIA occurring simultaneously with CD. This study reinforces the importance of taking into account the possible association of organ-specific autoimmune diseases during JIA course.

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#### References

1. Petty RE, Southwood TR, Baum J et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J Rheumatol* 1998;25:1991-1994.
2. Silva CA, Silva CH, Robazzi TC et al. Macrophage activation syndrome associated with systemic juvenile idiopathic arthritis. *J Pediatr (Rio J)* 2004;80:517-522.
3. Catassi C, Fasano A. Celiac disease diagnosis: simple rules are better than complicated algorithms. *Am J Med* 2010;123:691-693.
4. Miller ML. Clinical aspects of juvenile rheumatoid arthritis. *Curr Opin Rheumatol* 1997;9:423-427.
5. Lepore L, Martellosi S, Pennesi M et al. Prevalence of celiac disease in patients with juvenile chronic arthritis. *J Pediatr* 1996;129:311-313.
6. Stagi S, Giani T, Simonini G, Falcini F. Thyroid function, autoimmune thyroiditis and coeliac disease in juvenile connective tissue diseases. *Rheumatology (Oxford)* 2005;44:517-520.
7. Al-Mayouf SM, Al-Mehaidib AI, Alkaff MA. The significance of elevated serologic markers of celiac disease in children with juvenile rheumatoid arthritis. *Saudi J Gastroenterol.* 2003;9:75-78.
8. Lee YH, Rho YH, Choi SJ et al. The PTPN22 C1858T functional polymorphism and autoimmune diseases—a meta-analysis. *Rheumatology (Oxford)*. 2007;46:49-56.
9. Sloka JS, Phillips PW, Stefanelli M et al. Co-occurrence of autoimmune thyroid disease in a multiple sclerosis cohort. *J Autoimmune Dis* 2005;2:9.
10. Viken MK, Amundsen SS, Kvien TK et al. Association analysis of the 1858C>T polymorphism in the PTPN22 gene in juvenile idiopathic arthritis and

- other autoimmune diseases. *Genes Immun* 2005;6:271-273.
11. Alpigiani MG, Haupt R, Parodi S, Calcagno A, Poggi E, Lorini R. Coeliac disease in 108 patients with juvenile idiopathic arthritis: a 13-year follow-up study. *Clin Exp Rheumatol* 2008;26:162.
  12. Pohjankoski H, Kautiainen H, Kotaniemi K, Korppi M, Savolainen A. Autoimmune diseases in children with juvenile idiopathic arthritis. *Scand J Rheumatol* 2010;39:435-436.
  13. Ensari A. Gluten-sensitive enteropathy (celiac disease): controversies in diagnosis and classification. *Arch Pathol Lab Med* 2010;134:826-836.
  14. Choi SH, Kim YS, Chung JW et al. Serratia bacteremia in a large university hospital: trends in antibiotic resistance during 10 years and implications for antibiotic use. *Infect Control Hosp Epidemiol* 2002;23:740-747.