

## Co-existence of Crohn's disease and primary immune thrombocytopenia and its implications in treatment<sup>☆</sup>

### Coexistencia de enfermedad de Crohn y trombocitopenia inmune primaria y sus implicaciones en el tratamiento

Dear Editor:

Inflammatory bowel disease (IBD) is a multisystemic disease in which 30% of affected patients develop some type of extraintestinal manifestation (EIM). Extraintestinal manifestations may emerge at different stages during the disease, and may or may not be associated to the level of activity.<sup>1,2</sup>

Among the haematologic manifestations of IBD is primary immune thrombocytopenia (PIT), formerly known as idiopathic thrombocytopenic purpura. It is characterised by an isolated platelet count less than 100 000/mm<sup>3</sup> in the absence of an initiating cause. It is diagnosed by the exclusion of other causes in patients with persistent thrombocytopenia (Table 1).<sup>1,3,4</sup>

The association between IBD and PIT in children is rare, with prevalences estimated at 0.1–0.48%, and with a higher frequency of association with ulcerative colitis (UC) compared to Crohn's disease (CD).<sup>3,5</sup> We describe two cases of concurrent IBD and PIT, which are of interest considering the rarity of the association and the effects that the administered treatment may have on the course of disease.

#### Patient 1

Female aged 11 years with a history of CD (Paris classification A1a L2 B1 G0) diagnosed based on the Oporto criteria at age 4 years and undergoing maintenance treatment with azathioprine (AZA) at 2.5 mg/kg/day. At 9 years of age, while in clinical remission, she presented with ecchymosis and petechiae of sudden onset. Blood testing found a platelet count of 2000/mm<sup>3</sup>, and diagnostic tests were negative. The patient was given two doses of gammaglobulin (0.8 g/kg/dose) and intravenous corticosteroids (2 mg/kg/day) with no improvement, leading to diagnosis of PIT, and requiring maintenance therapy with gammaglobulin every three to four months (0.8 g/kg/dose) for persistent thrombocytopenia. Eighteen months after being diagnosed with PIT, the patient had a clinical and endoscopic relapse of CD (PCDAI 35; SES-CD, 6). Induction therapy was initiated with humanised anti-TNF factor alpha (adalimumab [ADA]) following the standard dosage with administration every two weeks (160, 80 and 40 mg by the subcutaneous route), after which the patient went into remission (PCDAI 0; faecal calprotectin [FC], 15 mg/kg). The patient responded

**Table 1** Causes of secondary PIT and thrombocytopenia.

Non-immune mechanism	Immune mechanism
Congenital thrombocytopenias, Bernard-Soulier syndrome, von Willebrand disease type IIb, MYH9-related disorders	Post-transfusion purpura and alloimmune thrombocytopenia
Bone marrow diseases: myelodysplastic syndromes, leukaemias, aplastic anaemia, bone marrow infiltration	Drug-induced immune thrombocytopenia Recent vaccination Infection by HIV, HCV. Other infections
Thrombotic thrombocytopenic purpura and other thrombotic microangiopathies	Association with other autoimmune diseases: lupus erythematosus, antiphospholipid syndrome, inflammatory bowel disease and thyroid disorders, among others
Chronic liver disease	Association with common variable immunodeficiency and autoimmune lymphoproliferative syndrome
Drug use (alcohol among others), natural medicine products and environmental toxins	Thrombocytopenia following haematopoietic stem cell or solid organ transplant
Drug-induced thrombocytopenia	Lymphoproliferative syndromes (CLL, NHL, HL, etc.)

favourably, with stabilisation of the platelet levels, and corticosteroid therapy was discontinued. At present, the patient is being treated with combined AZA-ADA, and has not required additional courses of gammaglobulin or corticosteroids 24 months after initiation of ADA. The patient is awaiting a control colonoscopy, based on which a switch to monotherapy will be considered.

#### Patient 2

Male aged 15 years with a CD diagnosis (A1bL2B1G0) undergoing maintenance treatment with mercaptopurine (6-MP) (1.5 mg/kg/day). Seven months after the diagnosis, while in clinical remission (PCDAI 0), the patient developed isolated thrombocytopenia (85 000/mm<sup>3</sup>). To rule out thiopurine-induced cytopenia (even though the rest of the cell counts and the thiopurine methyltransferase activity were normal), treatment was discontinued temporarily; the patient showed no improvement, with platelet levels reaching 9000/mm<sup>3</sup>, so treatment was resumed. The PIT diagnosis was reached after diagnostic test results came up negative. The patient was treated with gammaglobulin (0.8 g/kg/dose) and showed an initial favourable response, although he subsequently needed corticosteroid therapy (0.4–1 mg/kg/day) for maintenance. At present, 19 months following the PIT diagnosis, the patient remains

<sup>☆</sup> Please cite this article as: Crespo Madrid N, Ruiz Hernández C, Giraldo Escobar L, Pujol Muncunill G, Martín de Carpi J. Coexistencia de enfermedad de Crohn y trombocitopenia inmune primaria y sus implicaciones en el tratamiento. *An Pediatr (Barc)*. 2015;83:433–435.

**Table 2** Cases of Crohn's disease associated with primary immune thrombocytopenia described in the paediatric age group.

Case	Age at disease onset	Sex	Type of onset and time elapsed until first evidence of association	Localisation of CD	Platelets at onset of PIT	Treatment of PIT	Treatment of CD	Surgery	Remission of CD and PIT
1 Higuchi et al. <sup>3</sup>	11 years	M	CD 2.5 years before PIT	Colon	< 10,000/mm <sup>3</sup>	Gammaglobulin, corticosteroids	Mercaptopurine	No	Yes
2 Higuchi et al. <sup>3</sup>	2 years	F	CD 3 months before PIT	Ileocolonic	6000/mm <sup>3</sup>	Corticosteroids	5-ASA	No	Yes
3 Higuchi et al. <sup>3</sup>	5 years	F	PIT 6 years before CD	Ileocolonic	< 10,000/mm <sup>3</sup>	Gammaglobulin, corticosteroids	5-ASA, cyclosporin, tacrolimus	Splenectomy, colectomy	Yes
4 Manceñido et al. <sup>5</sup>	17 years	F	CD 6 years before PIT	Colon	< 10,000/mm <sup>3</sup>	Gammaglobulin, corticosteroids	5-ASA, corticosteroids	Yes Colectomy	Yes
5 Manceñido et al. <sup>5</sup>	14 years	F	PIT 6 months before CD	Colon	4000/mm <sup>3</sup>	Gammaglobulin, corticosteroids	5-ASA, azathioprine, corticosteroids, infliximab	No	Yes

CD, Crohn's disease; F, female; M, male; PIT, primary immune thrombocytopenia; AIT, autoimmune thrombocytopenia; 5-ASA, sulfasalazine.

in clinical remission with stable laboratory results (PCDAI 0; FC, 20 mg/kg) under low-dose corticosteroid treatment (0.1 mg/kg/day) with concurrent administration of mercaptopurine.

There are few descriptions of the association of CD and PIT in the literature (Table 2). The onset of PIT in association with IBD is variable, although based on the published cases it seems to occur more frequently after the diagnosis of IBD. Since the cases described in the literature involved UC more frequently than CD, we think it is worth noting that our patients with CD had exclusive colonic involvement, which supports the hypothesis that the inflammation of the colonic mucosa and/or the dysregulation of the local immune system may be associated with the development of PIT in these patients.<sup>3,5</sup>

Studies in adults have described cases of PIT refractory to conventional treatment that responded well to treatment with anti-TNF factor, and it has been hypothesised that the pathogenic mechanism involves the apoptosis of monocytes and macrophages (which produce TNF alpha, as do CD4 lymphocytes), with a decline in the anti-platelet antibodies produced by B lymphocytes.<sup>6</sup>

We believe that in the cases reviewed here, while conventional therapy was used when PIT first developed (gammaglobulin and corticosteroids), the adequate control of CD with anti-TNF factor agents in case 1 and thiopurines in case two allowed for the improved management and outcomes of PIT, without requiring further gammaglobulin doses. The additional option of discontinuing corticosteroid treatment in our patient treated with anti-TNF factor makes the possibility of escalating treatment in patient 2 attractive if his CD does not respond favourably.

To conclude, it could be said that the association between PIT and CD is rare. The treatment used for maintaining CD in remission can also achieve adequate control of PIT. Thus, aggressive treatments can be avoided, improving quality of life in these patients.

## References

- Dotson L, Hyams S, Markowitz J, LeLeiko S, Mack R, Evans S, et al. Extraintestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. *J Pediatr Gastroenterol Nutr.* 2010;51:140–5.
- Jose F, Garnett E, Vittinghoff E, Ferry G, Winter S, Baldassano R, et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2009;15:63–87.
- Higuchi L, Joffe S, Neufeld E, Weisdorf S, Rosh J, Murch S, et al. Inflammatory bowel disease associated with immune thrombocytopenic purpura in children. *J Pediatr Gastroenterol Nutr.* 2001;33:582–7.
- Monteagudo E, Fernández R, Sastrec A, Tolld T, Llorde A, Molina J, et al. Protocolo de estudio y tratamiento de la trombocitopenia inmune primaria. *An Pediatr (Barc).* 2011;74:414.e1–8.
- Manceñido M, Erdozain J, Pajares R, Paño J, González P, Navajas F, et al. Idiopathic thrombocytopenic purpura as an extraintestinal manifestation of Crohn's disease. *Gastroenterol Hepatol.* 2004;27:368–71.
- De Rossi T, Krauss N, Voll R, Nägel A, Weidenhiller M, Konturek P, et al. Long-term partial remission of autoimmune thrombocytopenia in a patient treated with the anti-tumor necrosis factor-alpha antibody infliximab for refractory fistulizing Crohn's disease. *Digestion.* 2008;78:195–200.

N. Crespo Madrid, C. Ruiz Hernández, L. Giraldo Escobar, G. Pujol Muncunill, J. Martín de Carpi\*

*Sección de Gastroenterología, Hepatología y Nutrición Pediátrica, Unidad para el Cuidado Integral de la Enfermedad Inflamatoria Intestinal Pediátrica, Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain*

\* Corresponding author.

*E-mail address:* [Javiermartin@hsjdbcn.org](mailto:Javiermartin@hsjdbcn.org) (J. Martín de Carpi).

## Hepatic hemangiomas: Spectacular response to treatment with propranolol<sup>☆</sup>

### Hemangiomas hepáticos: respuesta espectacular al tratamiento con propranolol

*Dear Editor,*

Infantile haemangiomas (IH) are the most common benign soft tissue tumour of infancy. They affect 1–2.6% of newborns and up to 10% by 1 year of age.<sup>1</sup> They typically present as solitary skin lesions. In some cases, IH may be multiple and involve extracutaneous organs, most commonly the liver.<sup>1,2</sup>

Hepatic haemangioma (HH) is the most frequent benign liver tumour in infancy,<sup>3</sup> with a preponderance of female infants.<sup>4</sup> They have been classified into three categories: focal, multifocal and diffuse.<sup>5</sup> Focal HHs usually consist of solitary and asymptomatic lesions and generally do not require intervention.<sup>1</sup> They seem to be equivalent to the skin lesions of rapidly involuting congenital haemangioma (RICH), and as happens in the latter condition, patients do not express the GLUT-1 glucose transporter that is usually found in IHs.<sup>1,5</sup> Multifocal and diffuse HHs are true HHs. Multifocal HH presents as multiple spherical lesions that may remain asymptomatic until their spontaneous resolution, and less frequently they may lead to heart failure secondary to arteriovenous or portovenous shunting. In diffuse HHs, there is near-total replacement of liver parenchyma, which may trigger abdominal compartment syndrome due to mass effect. It may also be associated to hypothyroidism due to high production of type III thyronine deiodinase.<sup>5</sup>

Traditionally, corticosteroids have been used as the first-line treatment of symptomatic HHs, alone or in combination with vincristine (VCR), which started to be used as an

<sup>☆</sup> Please cite this article as: Baena-Gómez MA, Priego Ruiz MP, González EM, Rosa MJ, Muñoz Sánchez RM. Hemangiomas hepáticos: respuesta espectacular al tratamiento con propranolol. *An Pediatr (Barc).* 2015;83:435–437.