Ileal Crohn’s disease in a woman with Hermansky-Pudlak syndrome

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SUMMARY

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder characterized by oculocutaneous albinism and platelet dysfunction. A subset of patients also show ceroid deposition, which can result in pulmonary fibrosis or granulomatous colitis. Whether this colitis may be considered Crohn’s disease is under debate. We report a case of a patient with HPS associated with inflammatory bowel disease which affected the distal small bowel but not the colon. Ileitis was severe, and recurred rapidly after surgery. Search for mutations in HPS1, ADTB3A, HPS3, HPS4 and for CARD15 were negative. Symptoms and ileal ulcerations which recurred after surgery were successfully treated with azathioprine and infliximab.

RÉSUMÉ

Maladie de Crohn iléale chez une femme atteinte du syndrome Hermansky-Pudlak

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Le syndrome d’Hermansky-Pudlak (HPS) est une affection rare autosomique récessive caractérisée par un albinisme et une dysfonction plaquettaire. Certains malades présentent aussi des dépôts céroïdes, une fibrose pulmonaire et une colite granulomateuse. Le lien entre la granulomatose colique et une éventuelle maladie de Crohn est discuté. Nous rapportons l’observation originale d’une malade atteinte d’HPS associée à une maladie inflammatoire chronique iléale et sans atteinte colique. L’ileïte était sévère et récidivait rapidement après une résection iléale chirurgicale. La recherche des mutations HPS1, ADTB3A, HPS3, HPS4 et CARD15 était négative. Les symptômes et lésions iléales ulcérées ayant récidivé après la chirurgie étaient traités par une association d’azathioprine et d’infliximab.

Introduction

Hermansky-Pudlak syndrome (HPS; MIM203300) is a rare group of genetically distinct disorders of vesicle formation characterized by oculocutaneous albinism, and bleeding diathesis due to a deficiency of dense bodies in platelets (HPS is the only reported cause for this association); in some cases, lysosomal accumulation of ceroid lipofuscin is also present [1, 2]. The albinism results in various degrees of pigment dilution, congenital nystagmus, a reduction of visual acuity, and iris transillumination [3, 4]. The storage pool deficiency occurs because of absence of dense bodies in platelets, resulting in a lack of a secondary platelet aggregation response. HPS patients often exhibit easy bruising and epistaxis, excessive menstrual and postpartum bleeding and prolonged bleeding during dental extractions and surgical procedures [5]. The absence of dense bodies, which are most readily seen on whole mount electron microscopy [5, 6], is the most critical element in diagnosing HPS. The third feature of HPS is the accumulation of ceroid lipofuscin, a lipid-protein complex of unknown etiology. It may be associated with pulmonary fibrosis (usually fatal by the fourth or fifth decade) [5, 7-9] and granulomatous colitis [5, 10-13].

Seven genes have been found to be associated with HPS. The most common subtype is HPS-1 (MIM 604982), which is a result of mutations in the HPS1 gene [14-16]. HPS-2 (MIM 603401) is due to mutations in ADTB3A [17-19]. HPS-3 (MIM 606118) to mutations in the HPS3 gene [20, 21], and HPS-4 (MIM 606682) to mutations in HPS4 [22, 23].

These HPS subtypes have different clinical features [24]. HPS-1 represents the classical disease, with all the above mentioned typical complications of HPS [5]. HPS-2 is usually responsible for oculocutaneous albinism, a bleeding diathesis, and childhood infections with neutropenia, but no pulmonary fibrosis or granulomatous colitis [18, 19]. HPS-3 shows mild oculocutaneous albinism and bleeding, with occasional colitis but no pulmonary fibrosis [20, 21]. HPS-4 disease resembles HPS-1 in severity including pulmonary fibrosis and colitis [23]. HPS-5 is associated with iris transillumination, variable hair and skin pigmentation, absent platelet dense bodies, but not with pulmonary fibrosis nor with granulomatous colitis [24].

Approximately 10-20% of HPS patients develop chronic granulomatous colitis but no case of isolated ileitis has been described so far. The average age of onset is in the second decade of life [5]. Histological lesions include areas of hyperemia and denuded epithelium and are very similar to Crohn’s disease [5, 10-12, 26]. Here we report a detailed case of a patient with HPS associated with inflammatory bowel disease (IBD), which affected only the small bowel.

Case report

Patient

A 34-year old Caucasian non-smoking woman was admitted in March 1999 with chronic diffuse abdominal pain, anemia and subacute
small bowel obstruction. Previous examinations had shown ileitis and led to the suspicion of Crohn’s disease. Her past history included an appendectomy in childhood, anal fistula in 1985, and cholecystectomy for lithiasis in 1987; she did not have frequent infections in childhood. Her uncle had albinism. Her symptoms had begun in 1985 with abdominal pain and hypochromic microcytic anaemia. In November 1998, an ileocolonoscopy disclosed terminal ileitis with deep and extensive ulcerations and stenosis in the terminal ileum. Biopsy samples from these lesions had shown chronic inflammation without granuloma. Small-bowel follow-through and abdominal computed tomography (CT) showed stenosis and wall thickening of the terminal ileum with adjacent dilated loops (figure 1). 5 amino-salicylate (5 ASA) and metronidazole were ineffective, and the patient refused steroid treatment.

Albinism was suspected as her skin was pale although her irises were pigmented. Hermansky Pudlak syndrome was then confirmed from platelet function studies. Impaired platelet aggregation induced by adenosine diphosphate (ADP) and no platelet aggregation with collagen were observed. The Mepacrine test [flow cytometry analysis] showed a reduced (30% of normal value) content of platelet dense bodies studied (i.e. a significant storage pool defect). Thorax CT and arterial blood gas measurements were normal. Resection of the ileal lesions (35 cm) and ileo-colonic anastomosis were performed in April 1999. Pathological examination of the ileo-caecal specimen disclosed transmural inflammatory infiltrate of the ileum and a normal colon. The lesions mainly affected the mucosa and sub-mucosa and were patchy as areas without lesions were present. No granuloma or ceroid deposits were found. The patient received 5-ASA 3 g/d after surgery. Three months later, she had recurrence of abdominal pain and diarrhoea and ileo-colonoscopy showed diffuse ileal ulcerations above the anastomosis (i.e. 4 lesions according to the Rutgeerts classification of postoperative recurrence) extending over 8 cm. Budesonide 9 mg per day was prescribed but proved ineffective. In October 2000, a combined treatment associating 5 mg/kg body weight (b.w.) infliximab infusion and azathioprine (225 mg/d i.e. 2.7 mg/kg b.w.) was started. All symptoms disappeared within one week for about 4 months. In February she had a relapse of diarrhoea and pain and a new infusion of infliximab which again induced quick remission. In 2002, the patient had slight diarrhoea; ileocolonoscopy showed that only three small ulcerations were present at the anastomosis (12 lesions according to Rutgeerts classification); the lesions which had been seen upstream previously were healed. Hysterecory was performed in 2003 because of chronic menorrhagia (myoma). At her last visit in November 2004, the patient who was still receiving azathioprine was in remission and endoscopy showed only two small aphthous ulcers in her terminal ileum with a normal anastomosis (11 lesions according to the Rutgeerts classification). Thorax CT scan and arterial blood gas measurements were normal in 2002 and 2004.

**Molecular analysis**

The CARD15/NOD2 variants were detected by polymerase chain reaction using allele specific primers labeled with fluorescent dye. gDNA was collected and genotyped for the 3 main variants of CARD15/NOD2 that are associated with CD (MIM 605956) as previously defined [27]. None of them were found.

**Discussion**

To our knowledge, this is the first case describing an HPS-associated IBD affecting the small bowel without colonic involvement. The patient had also had perianal fistula 15 years earlier. The diagnosis of HPS was established on the basis of albinism and platelet dysfunction with a storage pool defect. One uncle was affected with albinism.

Six cases of HPS-associated-IBD have been described in detail in the literature [5, 10-12] (table I). The colon was always involved; the clinical course was often severe as 3 of them required total colectomy. Pathological specimens showed non-necrotizing granuloma in all patients. Anal involvement was documented in one case. In two cases ileal lesions have been reported in association with colonic disease. In the first case, focal non-necrotizing granuloma was seen in the mucosa of the small intestine [10]. Another publication briefly described a small bowel stricture in a woman with HPS who had previously been treated with total colectomy [13]. She presented with abdominal pain and bloody diarrhea. Small-bowel study revealed a focal area of narrowing with mucosal ulceration in the proximal ileum. Small bowel resection was performed and pathological examination of the ileum specimen found non-caseating granulomas. Cereoid deposits (which appear when they are abundant as yellowish pigments using H&E or PAS-diastase staining) are sometimes but not always identified in the intestinal lesions [11]. In our case, we did not detect any cereoid deposits on the surgical specimen nor on ileal biopsies performed when the ileal disease recurred after surgery.

Our patient had had symptoms of chronic ileitis for several years, 5-ASA and budesonide were ineffective. Oral steroids...
Tableau I. – Cases of Hermansky-Pudlak Syndrome associated with intestinal bowel disease.
Observations publiées de syndrome d’Hermansky-Pudlak associés avec une pathologie intestinale.

<table>
<thead>
<tr>
<th>Disease location (N° of patients)</th>
<th>Age (years)</th>
<th>Histological findings</th>
<th>Molecular Analysis</th>
<th>Follow up</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis (4)</td>
<td>17 - 32</td>
<td>Granuloma and yellow pigment compatible with ceroid deposits [1]</td>
<td>ND</td>
<td>Subtotal colectomy (3)</td>
<td>10</td>
</tr>
<tr>
<td>Colitis (2) anal fissures (2) anal stricture (1)</td>
<td>3,7</td>
<td>Granuloma and yellow pigment compatible with ceroid deposits [1]</td>
<td>ND</td>
<td>6-mercaptopurine-cyclosporine (1) Last to follow up (1)</td>
<td>11</td>
</tr>
<tr>
<td>Colitis (1)</td>
<td>21</td>
<td>Ulneceration in the submucosa-inflammation in subserosa</td>
<td>ND</td>
<td>Colectomy</td>
<td>12</td>
</tr>
<tr>
<td>Ileocolitis (1)</td>
<td>38</td>
<td>Non necrotizing granuloma</td>
<td>ND</td>
<td>Colectomy and secondary proximal ileum resection</td>
<td>13</td>
</tr>
<tr>
<td>Ileitis (1)</td>
<td>34</td>
<td>No granuloma – No ceroid deposit</td>
<td>Undetermined</td>
<td>Ileo-caecal resection ileal recurrence Infliximab — azathioprine Present case</td>
<td></td>
</tr>
</tbody>
</table>

ND : not done.

were not used as the patient refused this treatment. Severe endoscopic and clinical postoperative recurrence occurred rapidly i.e. within 3 months after surgery. Azathioprine and infliximab injections were induced remission and azathioprine alone maintained remission and progressive mucosal healing for 5 years. No granuloma was found in the biopsy samples or on the ileocolonic specimen. The similarity between IBD associated with HPS and Crohn’s disease has been discussed in the literature; our case with ileal involvement further supports this hypothesis. It is also noteworthy that our patient had early recurrence of ileal lesions above the anastomosis (a usual feature of Crohn’s disease), and that infliximab and azathioprine induced remission and improvement of mucosal lesions.

Mutations in the CARD15 gene are observed in about 30% of the patients with Crohn’s disease; they were not searched for in previously reported cases of HPS and no mutation was found in our patient. Were may have failed to identify the genetic defect for HPS in our patient for two reasons. First, our SSCP screening method may have failed to identify a mutation because the mutation does not change the running pattern of the amplified DNA band. Second, the patient may have no mutation in one of the 4 HPS genes screened. During this study, three new genes causing HPS in humans have been discovered, HPS5, HPS6 and HPS7 [24, 28].

We conclude that HPS may be associated not only with colitis but also ileitis both of which mimick Crohn’s disease. Establishing a diagnosis of HPS and IBD is important for patients and clinicians so that complications can be identified. Gastroenterologists should HPS if there is complete or incomplete personal or familial albinism. Diagnosing haemorrhagic diathesis is important as well as early detection of pulmonary fibrosis since the antifibrotic agent, pirfenidone, has been shown to slow the decline in pulmonary function in HPS-1 patients [29].

REFERENCES


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