Complicated granulomatous colitis in a patient with Hermansky-Pudlak syndrome, successfully treated with infliximab

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Abstract

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder which is characterised by the triad of oculocutaneous albinism, platelet dysfunction and accumulation of ceroidlike pigment in tissues.

Complications of the syndrome, such as fatal pulmonary fibrosis, renal failure and cardiomyopathy have been described. Granulomatous colitis has been documented in several families with the HPS. The bowel disease of the HPS is a unique type of inflammatory bowel disease with clinical features suggestive of idiopathic ulcerative colitis (UC) and pathologic features suggestive of Crohn's disease.

We report a patient with HPS which was complicated by granulomatous colitis with perineal and rectovaginal fistulas refractory to antibiotics and azathioprine but dramatically responded to repeated infusions of infliximab. (Acta gastroenterol. belg., **2006**, 69, **213-216**).

Key words : Hermansky-Pudlak syndrome, granulomatous colitis, infliximab.

Introduction

Hermansky-Pudlak syndrome (HPS) is an inherited human disease affecting several intracellular organelles including melanosomes, platelet dense granules, and lysosomes (1-3). Abnormalities in these three organelles cause hypopigmentation, prolonged bleeding times, and in some patients ceroid deposition in several tissues including lung.

Associated clinical problems include severe visual deficiencies, haemorrhaging requiring repeated platelet transfusions, and fibrotic lung disease often leading to premature death in midlife. Unfortunately, only symptomatic treatment is available.

One of the well recognized complications of HPS is granulomatous colitis (9-13) representing an aggressive and progressive kind of bowel involvement. We report a patient with HPS which was complicated by granulomatous colitis with both superficial and complex fistulas refractory to conventional therapy but dramatically responded to repeated infusions of infliximab.

Case report

A 17-year-old female patient was referred to our hospital because of rectal bleeding, diarrhea lasting for more than two years and recent fecaloid vaginal discharge. Before her admittance to our department she was investigated in the pediatric gastroenterology unit of another state hospital.

Two years before a colonoscopic examination had revealed an active perineal fistula and macroscopic findings consistent with UC but histopathological examination disclosed active non-necrotising granulomatous colitis. An enteroclysis was performed and was reported to be normal.

She was put on steroid and 5- aminosalicylic acid treatment but as she did not respond well to this regimen the patient was believed to have UC complicated by tuberculosis (Tb) so anti Tb treatment was added and continued for one year although repeated faecal cultures and Ziehl-Neelsen stains had remained negative for acid-fast bacilli.

Under this regimen her diarrhea and rectal bleeding were persistent and she had to be operated two times for repeating perineal fistulas. At admission to our unit she was receiving azathioprine 75 mg/ d, sulfasalazine 3 g/ d and deflazacort 30 mg/ d.

On her physical examination she had normal vital signs. Her skin was pale and unpigmented and her hair had a whitish-blonde colour (Fig. 1). Her ophtalmological examination disclosed horizontal and rotatory nistagmus, her irises were gray-blue and had a slight pigmentation showing red reflex. The ophtalmoscopy disclosed a pale retina, a hypopigmented fundus. Besides these she had markedly reduced visual acuity.

On auscultation of the heart she had a mild mid-systolic murmur on the aortic valve but neither additional pathologic heart sounds nor murmurs on major arteries were noted. All peripheral pulses were palpable. Auscultation of the lungs revealed no pathology. Her bowel sounds were hyperactive on auscultation of the abdomen and she had a left lower quadrant tenderness without guarding, involuntary rigidity or rebound tenderness. She had no liver or spleen enlargement but rectal examination disclosed a low, superficial perineal fistula according to Cardiff Classification (4).

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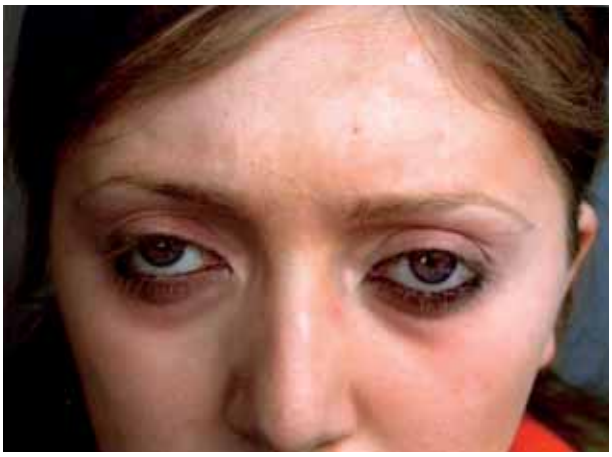

Fig. 1. — The 17-year-old albino female patient with blond hair and gray-blue eyes, remarkably nystagmus and strabismus.

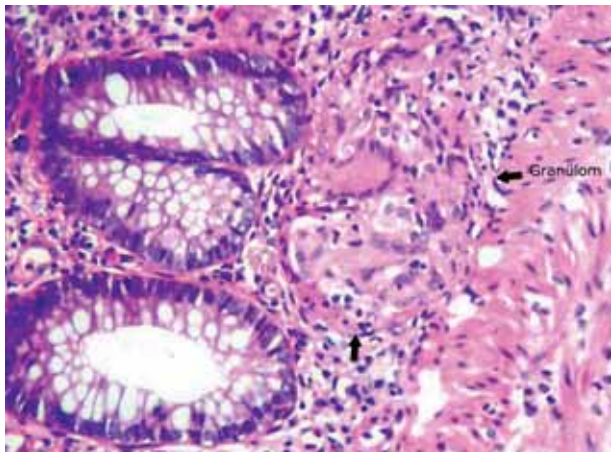

Fig. 2. — Non-necrotising granuloma formation is seen in colon biopsy specimen (HE × 400).

Her complete blood count was : hematocrit 25%, mean corpuscular volume 75 fl (normal, 80-95 fl), white blood cells 5800 / mm^3 (normal, 4000-10000), platelets 326000 / mm^3 (normal, 100000-450000), with microcytosis, hypochromia and anisocytosis of erythrocytes on peripheral smear. The erythrocyte sedimentation rate (ESR) was 35 mm / h ; C reactive protein (CRP) level was 26,9 mg / L (normal, 0-5). Her complete blood chemistry was normal but blood iron level was 21 mg / dl (normal, 27-144), iron binding capacity 223 mg / dl (normal, 200-450), ferritin 5,6 ng / ml (normal, 11-307) and her corrected reticulocyte count was 0,4%. Prothrombin, partial thromboplastin times were normal but she had a prolonged bleeding time of 11 minutes (normal, 3-9 min.). Urinalysis showed clusters of leucocytes and its culture was positive for *Escherichiae coli*.

A chest x-ray and plain abdominal radiograph revealed no pathology. A colonoscopy was performed and diffuse mucosal oedema, friability, fragility without rectal sparing in the presence of multiple pseudopolyps and ulcers varying in form and size were noted. The histopathological examination of biopsy samples disclosed severely active granulomatous colitis (Fig. 2). A subsequently performed fistulography showed a low, superficial perineal and a high, complex rectovaginal fistula according to Cardiff Classification (4). Thereafter, repeated faecal Ziehl-Neelsen stains, polymerase chain reaction assays and cultures remained negative for Tb.

The presence of refractory, complicated granulomatous colitis with oculocutaneous albinism and prolonged bleeding time led us to search for HPS. The electron microscopy revealed absence of dense granules in platelets (Fig. 3) and deposition of lipofuscin in macrophages (Fig. 4). In addition to these platelets of the patient showed abnormal aggregation with collagen.

After establishing the diagnosis of HPS the patient was investigated for pulmonary fibrosis but neither a high resolution tomography of thorax nor pulmonary function tests revealed any pathological findings.

For her active bowel disease and fistulas the dosage of azathioprine was raised to 100 mg / d, additionally metronidazole 500 mg. tid and ciprofloxacin 500 mg. bid were started when the steroid dosage was gradually tapered. Under this treatment she had only a mild improvement in the frequency of her diarrhea but both her perineal, rectovaginal fistulas persisted and the levels of acute phase reactants remained high.

Because of persisting fistulas the patient received infliximab perfusions at a dosage of 5 mg / kg initially and then repeatedly at the 2nd and 6th weeks. After the third infusion of infliximab she had a normal stool frequency, all her fistulas were closed completely and CRP, ESR returned to normal levels. A repeated colonoscopy showed normal macroscopic findings and the histopathology just revealed mild, non-specific colitis.

The patient received repeated infusions every two months and is under our close follow-up for more than two years without any further problems.

Discussion

HPS, first described in 1959 by Hermansky and Pudlak (5), is a rare autosomal recessive inherited disorder consisting of the following triad of symptoms : partial oculocutaneous albinism, platelet dysfunction and lysosomal deposition of ceroid lipofuscin pigment in tissues (5-6).

The albinism manifests as congenital nistagmus, iris transillumination, decreased visual acuity and variable degree of hypopigmentation of skin and hair. The platelet storage pool deficiency causes bleeding diathesis and there is a defect in the second wave of platelet aggregation. Ceroidlike lipofuscin accumulation, which is associated with systemic complications, has been observed in kidney, lung, bone marrow and other tissues (7). The most important complication of the disease is progressive pulmonary fibrosis which is characterised

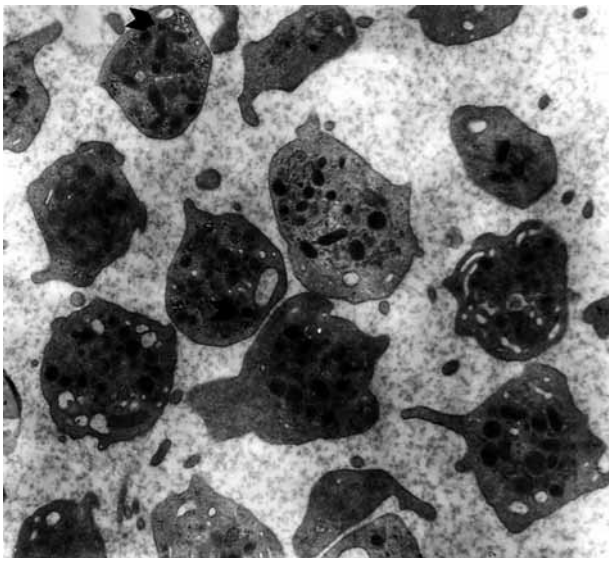

Fig. 3. — Electron micrograph showing platelets presenting stimulated morphology. The presence of very dense granules (arrows) is very difficult to observe (× 9500).

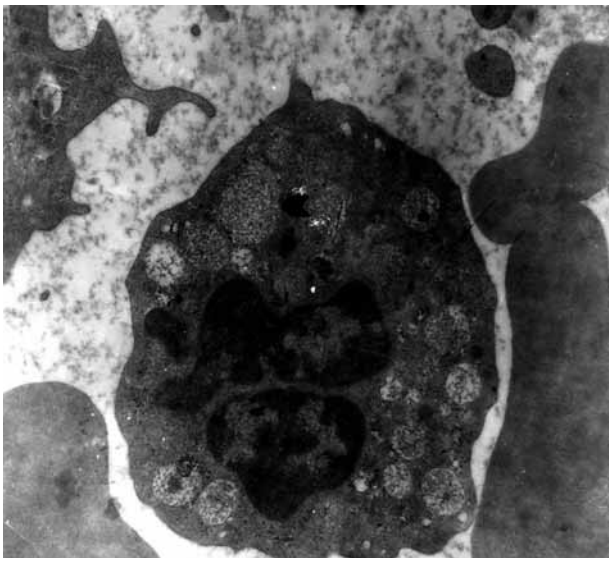

Fig. 4. — Electron micrograph of a lipofuscin (arrow) laden blood cell from buffy coat (× 4500).

by a restrictive component and progress to death in the fourth or fifth decade in most of the patients (6).

Although the disease occurs worldwide it is most common in north-western Puerto Rico thus its frequency is 1 in 1800 with a gene frequency of 1 in 18 approximately. The disease is very uncommon in Europe (8).

Another HPS associated complication is bleeding chronic granulomatous colitis which was first described as a part of the disease spectrum by Schinella *et al.* in 1980 (9), a finding which was supported by other authors as well (10-13). The colitis occurs approximately in 15% of patients with HPS (10), representing a unique type of inflammatory bowel disease with clinical features suggestive of UC and pathologic features suggestive of Crohn's disease (11).

The gene, causing HPS was first described in 1996 (14) and all studied Puerto Rican patients were homozygous for 16-bp duplication in exon 15. In Schinella's report (9) there were five Puerto Rican patients with colitis and four of them required surgical resection. In the series of Gahl *et al.* (10) 8 of 49 patients had bowel involvement and four of them had 16-bp duplication and three of them required subtotal or total colectomy whereas none of those without duplication required surgery. Thus these results indicate an aggressive and progressive kind of bowel involvement in HPS.

Our patient had a longstanding granulomatous colitis which was complicated by rectovaginal and perineal fistulas for which she was operated repeatedly. As Turkey is an endemic area for Tb she had received appropriate anti-Tb treatment for one year without any clinical response. After establishing the diagnosis of HPS we raised azathioprine to an appropriate dosage and started concomitant treatment with metronidazole and ciprofloxacin. After an observational period of two months we did not get any satisfying result so we decided to start infliximab treatment and under this regimen we obtained an excellent response.

We report this patient to let physicians remember HPS in albinotic patients with symptoms of inflammatory bowel disease. In light of this patient we conclude that infliximab might be a good treatment alternative for patients with HPS and concomitant bowel involvement.

To our knowledge, this is the first such a case of HPS treated with infliximab for its bowel involvement.

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