Campylobacter coli cultured from the stools of a patient with immunoproliferative small intestinal disease

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Abstract

Campylobacter has been associated with immunoproliferative small intestinal disease (IPSID), on the basis of 16S rDNA sequencing, *in situ* hybridization, and immunohistochemistry. Here, for the first time, we have cultured *Campylobacter* from the stools of a patient with IPSID. Phenotypic analysis and whole genome sequencing identified *Campylobacter coli*. PCR on a IPSID tissue biopsy sample was positive for *Campylobacter coli* and negative for *Campylobacter jejuni*. These findings further support a causative role for *Campylobacter* in the development of IPSID.

Keywords: α-Heavy-chain disease, *Campylobacter*, immunoproliferative small intestinal disease, IPSID, lymphoma
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Introduction

Immunoproliferative small intestinal disease (IPSID) is a rare B-cell mucosa-associated lymphoid tissue (MALT) lymphoma that involves mainly the proximal small intestine, and is characterized by the synthesis of a monotypic truncated immunoglobulin α-heavy chain lacking associated light chains [1,2]. It is mainly observed in young individuals in developing countries. On the basis of 16S rDNA sequencing, *in situ* hybridization, and immunohistochemistry, IPSID has been associated with *Campylobacter* [3,4]. We report here a new case of IPSID associated with *Campylobacter*, and the first from which it was cultured. Phenotypic analysis and whole genome sequencing identified *Campylobacter coli*. PCR on an IPSID tissue biopsy sample was positive for *C. coli* and negative for *Campylobacter jejuni*. These findings further support a causative role for *Campylobacter* in IPSID development.

Case Report

A 31-year-old man originating from Guinea and living in France for 3 years presented on 15 October 2011 with a 5-month history of severe diarrhoea, abdominal pain, and weight loss of 4 kg, without fever. Two months earlier, he had returned from a 1-year visit to Guinea, where his symptoms had started. Physical examination showed a sensitive caecal mass, no peripheral adenopathy, and no hepatosplenomegaly. Serological investigation for human immunodeficiency virus-1 gave negative results, and the blood C-reactive protein level was 133 mg/L. Parasitological examination of stools gave negative results, and stool cultures were positive for *Campylobacter*,

identified as *C. coli* on the basis of a negative hippurate assay result, and confirmed by whole genome sequencing. A computed tomography scan showed a caeco-ileitis and numerous coeliac, mesenteric and retroperitoneal supra-centimetre adenopathies.

The patient received azithromycin 500 mg daily without clinical efficacy, and signs of malabsorption appeared (hypoalbuminaemia and sideropenic anaemia). A colonoscopy was performed, and disclosed diffuse small nodules at the mucosal surface with red petechial spots in the left colon, and a large and infiltrated nodule with enlarged folds and incomplete stenosis in the ileocaecal junction (Fig. 1a). Histological examination showed a dense and diffuse lymphoid infiltrate composed of numerous plasma cells and lymphocytes with centrocyte features, without cytonuclear atypia, which invaded the glandular epithelium from place to place to form typical lymphoepithelial lesions (Fig. 1b). No sign of transformation to high-grade large B-cell lymphoma was observed. Immunohistochemical investigation identified lymphoid infiltrating cells as strongly positive for CD20, positive for Bcl2, and negative for Bcl6, CD5, and CD3. The lymphoid infiltrate was positive for α-heavy chain, but negative for κ-light chain and λ-light chain (Fig. 1c). Investigation of clonality by PCR of total DNA extracted from ileocaecal biopsies gave negative results for B-cells and T-cells. Immunoelectrophoretic analysis of serum did not demonstrate anti-α-heavy-chain precipitins without associated light chain. The total serum IgA level was 3.5 g/L. Oesophagogastroduodenoscopy gave normal findings.

In order to investigate the presence of *C. coli* within IPSID ileocaecal lesions, we performed a PCR specific for *C. jejuni* and *C. coli* with the CCCJ609F and CCCJ1442R oligonucleotides [5], amplifying the 16S rRNA (*rrs*) sequence, and a second PCR amplifying the *C. coli* aspartate kinase gene, with the CC519R and CC18F oligonucleotides [5]. Both PCRs were positive. In contrast, a *C. jejuni*-specific PCR amplifying the hippuricase gene was negative. Together, these results support the presence of *C. coli* and the absence of *C. jejuni* in the IPSID tissue sample of this patient.

On the basis of the clinical presentation and typical histopathological features, a diagnosis of ileocaecal IPSID was made. The absence of anti-α-chain precipitin led to the diagnosis of non-secreting IPSID. The patient received antimicrobial combination therapy with amoxycillin, metronidazole and clarithromycin for 2 months, and this led to the complete disappearance of diarrhoea. Stool cultures performed after the completion of antimicrobial therapy did not isolate *Campylobacter*.

Three months later, because of asthenia, weight loss, and a persistent caecal mass, the patient underwent abdominal positron emission tomography, which showed numerous hypermetabolism foci at the caecal, mesenteric and splenic levels (Fig. 1d). A hemi-right colectomy was performed, and histopathological analysis led to the diagnosis of large B-cell non-Hodgkin lymphoma (NHL), which was strongly IgA-positive and negative for light chains. Bone marrow biopsy sampling did not show NHL extension. While receiving a chemotherapy course consisting of a first round of cyclophosphamide and three consecutive rounds of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, the patient presented with an upper occlusive syndrome and a new lesion of the fourth duodenum. He received second-line therapy consisting of four rounds of rituximab, dexamethasone, cytarabine, cisplatin, and prednisone. He died in the weeks after completing his second-line treatment in the context of profound febrile neutropenia and acute renal failure secondary to obstruction by tumour progression, before he could receive an allograft from his human leukocyte antigen-compatible brother.

Discussion

Since the first description of α-chain disease in 1968 by Seligmann *et al.* in a young Syrian woman [1], approximately 570 cases, also referred as Mediterranean lymphoma or IPSID, have been published. IPSID mainly occurs in developing

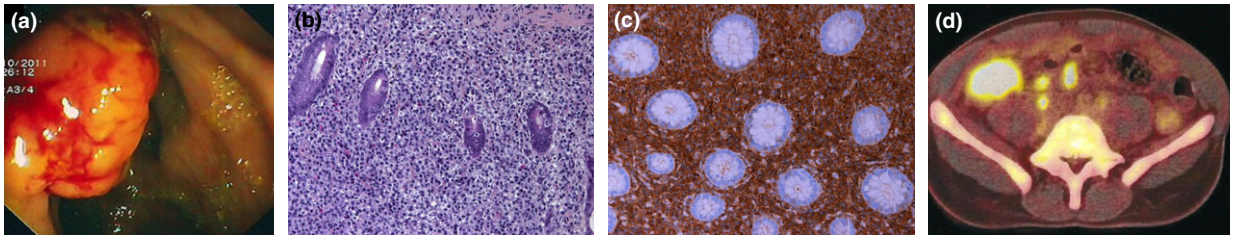

FIG. 1. (a) Endoscopic aspect of immunoproliferative small intestinal disease (IPSID) tissue at the time of diagnosis. (b) Haematoxylin, eosin and Safran staining. Intestinal lamina propria infiltration by plasma cells and admixed small lymphocytes can be seen. Lymphoepithelial lesions are present. Original magnification: ×10. (c) Immunohistochemical staining for α-heavy chain. Infiltrating lymphoplasmacytes express cytoplasmic α-heavy chain. Original magnification: ×20. (d) Positron emission tomography image at the time of relapse.