Italian Journal of Medicine (2011) 5, 124—127

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CASE REPORT

Hyposplenism as a cause of pneumococcal meningoencephalitis in an adult patient with coeliac disease

Iposplenismo come causa di meningoencefalite pneumococcica in un paziente adulto con malattia coeliaca

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Received 29 November 2010; accepted 21 February 2011
available online 3 April 2011

KEYWORDS
Coeliac disease;
Hyposplenism;
Streptococcus pneumoniae
meningoencephalitis.

Summary
Introduction: Coeliac disease can be associated with hyposplenism and splenic atrophy, which may increase the patient's risk for fatal infections caused by *Streptococcus pneumoniae* or *Pneumococcus*. It is general opinion that many more patients with coeliac disease have died from hyposplenism-related infections than those reported in literature.
Case report: A 62-year-old woman with recently diagnosed coeliac disease was hospitalized with high fever, disorientation, and nuchal rigidity. Cerebral computed tomography was negative. Laboratory tests showed an elevated leukocyte count and very high levels of C reactive protein. The cerebrospinal fluid (CSF) contained an increased number of mononuclear cells associated with a low glucose level and high protein concentrations. The CSF culture was positive for *Streptococcus pneumoniae*. Neurological conditions rapidly deteriorated with the onset of coma, and magnetic resonance imaging of the brain revealed initial signs of encephalitis extending above and below the tentorium. Abdominal ultrasonography disclosed splenic hypotrophy that raised the suspicion of hyposplenism. The diagnosis of hyposplenism was confirmed by demonstration of Howell-Jolly bodies in a peripheral blood smear.
Discussion: This is the first reported case of pneumococcal meningoencephalitis caused by splenic hypofunction in a patient with coeliac disease. When coeliac disease is diagnosed with

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1877-9344/$ — see front matter
doi:10.1016/j.itjm.2011.02.005

a marked delay in an elderly patient, spleen function should always be assessed. If impaired, the patient should undergo vaccination with pneumococcal conjugate vaccine to prevent pneumococcal infections.

Introduction

Coeliac disease (CD) is an immune-mediated disorder of the small intestine triggered by the ingestion of gluten in genetically susceptible individuals. Although it was initially considered a disorder developing almost exclusively in children or young individuals, it now appears evident that CD can manifest even in adult or advanced ages or remain misdiagnosed for many years due to the lack of symptoms [1].

The clinical manifestations of untreated CD range from significant malabsorption of multiple nutrients, with diarrhoea, steatorrhea, weight loss, and the consequences of nutrient depletion (i.e., hypoalbuminemia, anaemia and metabolic bone disease) to the evidence of the malabsorption of a single nutrient (i.e., iron, folate and/or vitamin D deficiency) in the absence of any gastrointestinal symptoms.

Furthermore, CD patients carry an increased risk of bacterial infections and sepsis [2]. Because the spleen plays a crucial role in the generation and survival of immunoglobulin (IgM)-producing memory B cells that are responsible for protection against encapsulated bacteria, the hyposplenism and splenic atrophy that may occur in CD patients represent a predisposing factor to the development of fatal infections caused by Streptococcus pneumoniae or Pneumococcus [3]. Although the presence of splenic hypofunction in CD is generally associated with a poor prognosis, its clinical relevance continues to be overlooked. Thus, general opinion holds that many more CD patients may have died from hyposplenism—related infections than those reported in literature [4,5].

We here describe the first known case of an adult woman with a recent CD diagnosis who developed pneumococcal meningoencephalitis leading to a severe impairment of neurological functions.

Case report

A 62-year-old woman with CD was referred to the Emergency Department of our Hospital for the abrupt onset of high fever and mental disorientation. One month before, she had been diagnosed as having CD due to a positive serology [IgA anti-endomysial (EmA) and tissue transglutaminase antibodies (tTGA) at medium-high titre], a typical histological pattern [partial villous atrophy — lesion type 3b according to Marsh-Oberhuber classification [6]] and a clinical picture characterized by abdominal pain, constipation and vomiting. Laboratory tests did not show any abnormality except for a marked thrombocytosis (platelet count: 684.000 mm^3). She immediately started to follow a strict gluten-free diet (GFD).

On admission to the Emergency Department, her Glasgow Coma Scale (GCS) was 13/15, and the neurological examination revealed neck stiffness. Hemodynamic and respiratory parameters were stable and within the normal range. Laboratory tests revealed the persistence of raised platelets, an elevated leukocyte count (12.56 x 10^3/mmc with 89.1% neutrophils) and C reactive protein (35.26 mg/dl). Renal and hepatic function, serum electrolytes, metabolic parameters and coagulation tests were within normal limits. The analysis of the cerebrospinal fluid (CSF) revealed the prevalence of mononuclear cells associated with low glucose and high protein concentrations, while a computed tomography (CT) scan did not show brain alterations. She was admitted to the Department of Infectious Diseases and treated empirically with ceftriaxone (2 grams b.i.d.) and levofloxacin (500 mg b.i.d.) together with desametasone (4 mg q.i.d.). On the fourth day, the neurological conditions rapidly deteriorated with the onset of coma (GCS 5/15). The patient was transferred to the Intensive Care Unit and then intubated, mechanically ventilated and maintained on the same antibiotic regimen, as the CSF culture was positive for *Streptococcus pneumoniae* sensitive to levofloxacin and cefotaxime [Minimum Inhibitory Concentration (MIC) was 1 μgr/mL and 0.25 μgr/mL for levofloxacin and cefotaxime, respectively, according to the CLSI reference]. A second CT and a magnetic resonance (MR) of the brain showed initial encephalitis extending both above and below the tentorium (Figure 1). Intravenous immunoglobulins were added to the treatment.

The following day, neurological conditions remained stable, and the patient regained spontaneous breathing and was tracheotomised. A second lumbar puncture was performed on the 8th day of treatment, and the CSF culture was negative. An abdominal ultrasound showed a splenic hypotrophy (diameter, 5.2 cm; area, 10.67 cm^2) (Figure 2), raising the

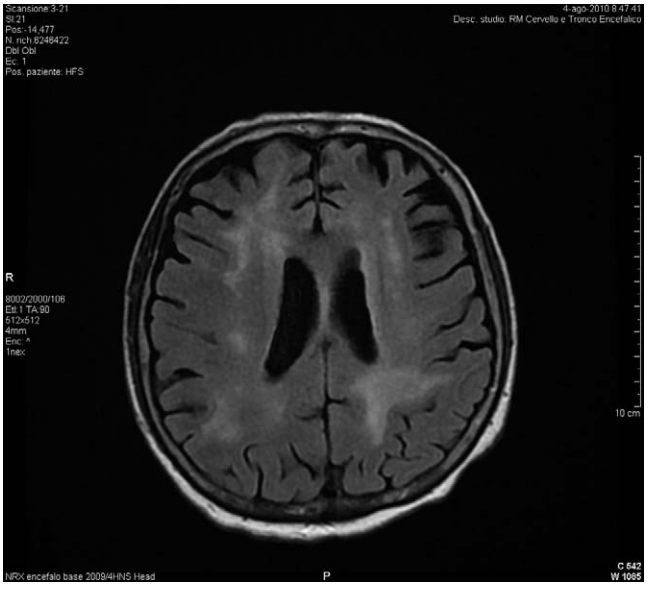

Figure 1 Brain magnetic resonance imaging (MRI) scan showing multiple areas of high intensity patterns within the white matter bilaterally suggestive of inflammatory encephalitis.

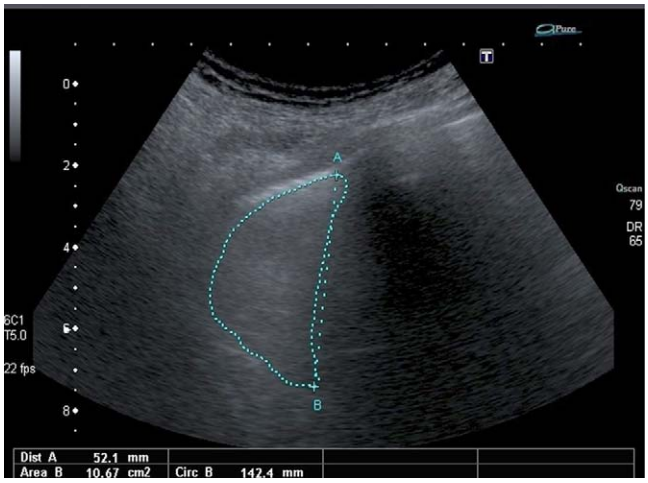

Figure 2 Abdominal ultrasound showing reduced spleen size (diameter, 5.2 cm; area, 10.67 cm^2).

suspicion of a condition of hyposplenism. The finding of Howell-Jolly bodies in the erythrocytes on a peripheral blood film confirmed the diagnosis of splenic hypofunction (Figure 3).

When the patient was transferred to the Department of Rehabilitation after 17 days of stay in the Intensive Care Unit, the neurological conditions were not improved (GCS 5/15), while the cardiovascular and respiratory functions were normal. A third CT scan revealed the persistence of the neurological lesions. The patient underwent vaccination with a pneumococcal conjugate vaccine in order to prevent other pneumococcal infections.

At present (after two months of physical rehabilitation), her clinical conditions have significantly improved, and the patient has partially regained her motor autonomy with assisted walking, although her mental function is still significantly compromised. The relatives of the patient gave written informed consent to the publication of the present case report.

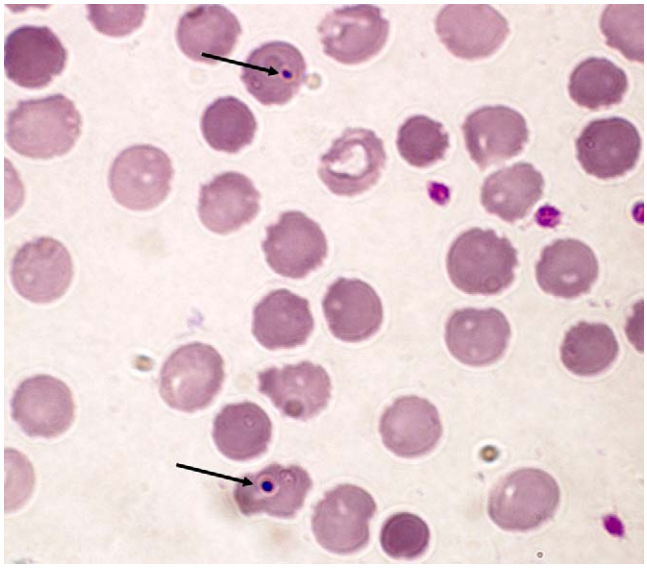

Figure 3 Peripheral blood smear showing the presence of Howell-Jolly bodies (see arrows) in the erythrocytes (characteristic features of functional hyposplenism).

Discussion

Although some cases of overwhelming pneumococcal infection and sepsis in patients with CD and hyposplenism have already been reported [4,5], we describe, to the best of our knowledge, the first case of pneumococcal meningoencephalitis in an adult patient with sprue and hyposplenism.

Splenic hypofunction has been classified as a complication of CD predisposing the patient to autoimmunity, lymphoma and pneumococcal septicaemia [1]. The occurrence of hyposplenism in CD, which can sometimes manifest with spleen atrophy, is very high with a prevalence varying from 20% to 60% in the different series of patients studied and is much more frequent in adults than in children [3,7–9]. In CD patients, hyposplenism appears to be closely related to the development of autoimmune disorders and it is found in more than 50% of CD patients with insulin-dependent diabetes mellitus, autoimmune thyroiditis and connective tissue disorders. Moreover, splenic hypofunction has been reported in 80% of CD patients with lymphoma, refractory sprue or ulcerative jejuno-ileitis. In CD patients without associated autoimmune disease and the above-mentioned life-threatening complications, the prevalence of hyposplenism is far lower (19%) [3].

Splenic hypofunction and spleen atrophy predispose the patient to severe infections because the spleen plays a crucial role in the generation and survival of IgM-producing memory B cells that are responsible for protection against infection by encapsulated bacteria such as Pneumococcus [3]. Although the epidemiological data on bacterial infections and sprue are still scarce, it is widely accepted that CD patients present a greater risk of pneumococcal infection than healthy individuals, although the risk is not as high as in those with splenectomy [10]. Thus, patients who are splenectomised or have impaired splenic function should be immunised by the administration of a pneumococcal conjugate vaccine [1,3,10].

The pathogenesis of splenic hypofunction in CD remains unknown. The duration of exposure to gluten due to a marked delay in CD diagnosis is considered the main factor influencing the occurrence of hyposplenism and its severity [3]. In some patients, splenic hypofunction is related to generalized lymph node atrophy, and it has been suggested that it is an expression of a more widespread atrophy of the lymphoreticular system [11]. This hypothesis is not supported by the demonstration that Kuppfer cell function in patients with functional hyposplenism, assessed by the clearance of microaggregated albumin, was similar to that of control splenectomised subjects [12]. Increased levels of circulating immune complexes, frequently found in CD, have been considered a possible cause of hyposplenism through a functional blockade of the splenic reticulo-endothelial system, but the very low prevalence of hyposplenism in childhood CD, which is characterized by the highest levels of immune complexes, does not support this hypothesis [13].

Splenic function must be assessed with appropriate tests. A commonly used method is to count ''pitted'' erythrocytes (''red cells with membrane escavation'') by interference

contrast microscopy [14]. A pitted erythrocyte count of more than 2% to 4% is consistent with a diagnosis of hyposplenism. Unfortunately, this test is available only in a few laboratories. Alternatively, the finding of Howell-Jolly bodies in the erythrocytes on a peripheral blood smear is an important clue to the diagnosis of functional hyposplenism [15]. However, they may not be evident in patients with milder forms of hyposplenism. Splenic hypofunction can also be demonstrated by performing a 99 tc-labelled radiocolloid scan of the spleen [3]. Moreover, the finding of a marked reduction of the spleen size in a routine abdominal ultrasound is consistent with a suspicion of hyposplenism that should be confirmed by the above-mentioned procedures.

Regarding this patient, CD was diagnosed in the 7th decade of age suggesting a very prolonged exposure to gluten as a possible explanation of splenic hypofunction. The only abnormality of routine tests was thrombocytosis; in CD, this is more frequently secondary to inflammatory mediators (with an expected normalization after GFD) or, less frequently, secondary to iron deficiency or an expression of splenic hypofunction [9]. Splenic hypofunction was not ruled out in our patient at the time of CD diagnosis, even though it seemed highly improbable due to the good general condition of the patient, excluding major CD complications, and the absence of associated autoimmune disorders, which are possible clues of splenic hypofunction. The rapid occurrence of pneumococcal septicaemia with meningoencephalitis did not allow us to monitor the behaviour of the thrombocytosis and to investigate for spleen dysfunction. The suspicion of a coexistent hyposplenism in our patient became evident when the CSF turned out to be positive for *Streptococcus pneumoniae,* and an abdominal ultrasound showed a reduced size of the spleen. The presence of functional hyposplenism was then confirmed by the finding of Howell-Jolly bodies in the blood smear.

This case report should teach us that all patients diagnosed as coeliacs in the adult age, and particularly in the elderly, should be evaluated for the possible presence of hyposplenism, even when in the clinical picture, the absence of associated autoimmune disorders and the normality of laboratory tests do not support this complication. To assess this CD complication, it is enough to verify the presence of Howell-Jolly bodies in a peripheral blood smear, keeping in mind that this procedure must be specifically requested to haematologists.

Because pneumococcal septicaemia in its different clinical manifestations is life-threatening, in all cases with well-documented hyposplenism, it is mandatory to perform immediate vaccination with a pneumococcal conjugate in order to protect CD patients from pneumococcal sepsis.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgements

The authors wish to thank Dr Nicola Vianelli from the Haematology Unit, Dr Mariangela Taricco and Dr Mario Gaiba from the Rehabilitation Unit and Prof. Pierluigi Viale from the Infectious Disease Unit of St. Orsola-Malpighi Hospital for their helpful assistance in the evaluation and treatment of the patient described in this paper.

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