

## Hypogammaglobulinemia associated with nodular lymphoid hyperplasia of the intestine and pernicious anaemia

### Hypogammaglobulinémie associée à une hyperplasie nodulaire lymphoïde et une anémie de Biermer.

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#### RÉSUMÉ

**Prérequis :** L'hyperplasie nodulaire lymphoïde du tube digestif, les broncho-pneumopathies infectieuses à répétition et les maladies auto-immunes sont des complications bien connues du déficit immunitaire commun variable.

**But :** L'objectif de ce travail est de discuter à travers cette observation les présentations cliniques ainsi que les diagnostics différentiels de l'hyperplasie nodulaire et lymphoïde associée à une hypogammaglobulinémie.

**Observation :** Nous rapportons l'observation d'un jeune patient aux antécédents de pneumopathies à répétitions, présentant une hyperplasie nodulaire lymphoïde, une anémie de Biermer associées à un déficit immunitaire commun variable.

**Conclusion :** Le diagnostic d'une hyperplasie nodulaire lymphoïde peut être difficile. En effet, l'aspect pseudo-polypoïde des lésions intestinales faisait suspecter initialement une polypose.

#### Mots-clés

Hyperplasie nodulaire lymphoïde, anémie de Biermer, déficit immunitaire commun variable.

#### SUMMARY

**Background:** Nodular lymphoid hyperplasia of the gastrointestinal tract, recurrent acute pulmonary infections and autoimmune disease are well-recognized complications of common variable immunodeficiency.

**Aim :** We aimed to focus on clinical presentation and differential diagnosis of diffuse nodular lymphoid and hyperplasia of the gastrointestinal tract coexisting with hypogammaglobulinemia.

**Case-report:** We report the case of nodular lymphoid hyperplasia associated with pernicious anaemia in a young man with hypogammaglobulinemia and a long history of pulmonary infections.

**Conclusion:** The considerable point was a mismatch primary clinical diagnosis of familial adenomatous polyposis, due to prominent polyp-like endoscopic appearance of the lesions throughout the digestive tract.

#### Key - words

Nodular lymphoid hyperplasia, common variable immunodeficiency, pernicious anaemia

Common variable immunodeficiency (CVID) is a syndrome characterized by hypogammaglobulinemia with phenotypically normal B cells. It is also known as acquired hypogammaglobulinemia because of a generally later age of onset of infections. The majority of patients have at least one episode of pneumonia prior to diagnosis. The age at the onset of symptoms is variable, ranging from childhood to late adulthood, with some evidence of a bimodal distribution demonstrating peaks between 1 and 5 years and 18 and 25 years. The gastrointestinal manifestations of CVID are variable and tend to mimic diseases like chronic-atrophic gastritis, chronic giardiasis, intestinal malabsorption, nodular lymphoid hyperplasia (NLH), and pernicious anaemia. Biopsy and resection specimens from the small bowel demonstrate a wide range of morphologic changes, from marked villous atrophy and increased lymphocytes in surface epithelium resembling celiac sprue, to nodular lymphoid hyperplasia and lymphoma [1]. Patients may first present with symptoms and signs of diarrhoea, malabsorption, and weight loss. Malabsorption and diarrhoea occur in 9 to 40% of patients with CVID. In those with diarrhoea, an infectious aetiology is rarely confirmed [2]. Many studies continue to confirm a high prevalence of inflammatory, malignant, and infectious gastrointestinal disorders in patients with CVID.

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### CASE REPORT

A twenty-four-year old man with a history of recurrent pulmonary infections during childhood, was first admitted for evaluation of persistent symptoms of abdominal pain, unremitting diarrhoea, productive cough, and fever. Physical examination revealed a good general health; the body mass index was 20 Kg/m<sup>2</sup>. Admission vital signs were normal. Rhonchi and crepitant rales were heard in both lungs. The abdomen was soft without hepatomegaly, splenomegaly or other abnormal mass. No mucosal or skin lesions were seen. There was no adenopathy or hyperplasia of pharyngeal lymphoid tissue. There were any palpable lymph nodes. The lower limbs were free of oedema.

Laboratory investigations revealed a Haemoglobin level of 11.2 g/dl. Hematocrit was 34%. The mean corpuscular volume (MCV) was 110/micro m<sup>3</sup>. Reticulocyte count was 36000/mm<sup>3</sup>. The white blood cell count was 5100/mm<sup>3</sup> with a normal differential. The sedimentation rate was 12/h. The serum albumin was normal (39 g/l), but protein electrophoresis showed hypogammaglobulinemia. All immunoglobulin classes were decreased (IgG 1.9g/l; IgM 0.23 g/l; IgA 0.009g/l). The examination of the bone marrow showed megaloblastosis. Serum vitamin B12 was low (< 60 pg/ml). Serum iron and serum folates were normal. Prothrombin time, serum calcium and serum cholesterol were normal. Microscopic examination of the feces didn't reveal *Giardia lamblia*. Chest X-ray showed bilateral bronchiectases predominant in the lower lobes and on the right side. Endoscopy of the upper gastrointestinal tract showed gastric atrophy and a nodular appearance of duodenal mucosa. Multiple biopsies were performed revealing an atrophic gastritis, helicobacter pylori negative and a nodular lymphoid hyperplasia of the duodenum. Colonoscopy

demonstrated diffuse polyposis involving the colonic mucosa and the ileum. Numerous biopsy specimens showed nodular infiltrates of mononuclear cells occupying the mucosa including the lamina propria. The infiltrates were composed of typical lymphocytes. There was no appearance of mitotic activity. The epithelium was minimally and superficially eroded but otherwise normal. A computed tomography, performed to find deep adenopathy, was normal. The diagnosis of intestinal nodular lymphoid hyperplasia associated with hypogammaglobulinemia and pernicious anaemia was made.

The patient was treated with intravenous human immunoglobulin. He had also received cyanocobalamin intramuscularly 1000 µg/week for 1 month and monthly thereafter. Antibiotics were given for the bronchopneumopathy.

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### DISCUSSION

Although somewhat heterogeneous in clinical presentation and manifestations, CVID is recognized as the most prevalent primary immunodeficiency disease, excluding selective IgA deficiency. It is characterized by hypogammaglobulinemia and recurrent sinopulmonary infections, chronic diarrhoea, with an enhanced risk for malignancy, granulomatous disease, and joint involvement [3,4,5]. There is a high prevalence of inflammatory, malignant, and infectious gastrointestinal disorders in patients with CVID. These include nodular lymphoid hyperplasia, which was reported in our case, sprue-like illness with flat villi, pernicious anaemia, giardiasis, and non-specific malabsorption. Defects in cellular immunity, rather than antibody deficiency alone, appear to predispose patients to such illnesses [6].

Nodular lymphoid hyperplasia is a term used to describe polypoid masses of hypertrophied intestinal lymphoid tissue of the gut. The lesions range in size from small nodules to obstructing masses. They are observed in the stomach, colon, and small intestine. The significance of these hyperplastic lymphoid masses in the gut is unknown [7]. This entity was first reported in 1958 and described in detail by Hermans in 1966. Initially this syndrome was considered to represent a unique immune defect, but subsequent studies have shown that nodular lymphoid hyperplasia occurs in patients with widely differing immunoglobulin deficiencies. The syndrome is usually characterized by severe diarrhoea, deficiency of serum immunoglobulin and multiple hyperplastic lymphoid nodules in the small bowel biopsy specimens. It can be associated with chromosomal abnormality, usually, with X chromosome [7].

Gastrointestinal symptoms are common in hypogammaglobulinemia, but are usually a lesser problem than recurrent sinopulmonary infections. Diarrhoea is the most frequent gastrointestinal symptom and has been shown to be associated with jejunal mucosal abnormalities, lactase deficiency, colitis, bacterial overgrowth and parasitic infestation, especially with *Giardia lamblia*. In most cases the severity of gastrointestinal symptoms is related to the giardiasis and eradication of the parasites by adequate antibiotics is followed by clinical and histologic improvement.

Microscopically lesions of lymphoid nodular hyperplasia occur in the mucosa and cause deformity of adjacent villi and crypts. The lymphoid nodules consist of an orderly arrangement of small mature lymphocytes surrounding large active germinal centers. Differentiation

between this lesion and lymphoma is usually not difficult. Plasma cells are usually very few or totally absent. In some cases lesions resemble those seen in celiac disease. Whereas in celiac disease there are increased numbers of plasma cells in the small bowel lamina propria, in hypogammaglobulinemic sprue this region of the mucosa is almost devoid of plasma cells, which are replaced by numerous small lymphocytes and some histiocytes and eosinophils. Incubation of sections of small bowel mucosa from celiac disease patients with fluorescein conjugated antibodies to IgA demonstrates large sheets of IgA containing cells filling the lamina propria; in hypogammaglobulinemic sprue, IgA containing cells are extremely rare. The differential diagnosis of nodular lymphoid hyperplasia with hypogammaglobulinemia includes multiple lymphomatous polyposis, adenomatous polyps, with or without carcinomatous degeneration; familial adenomatous polyposis (FAP); and syndromes of Peutz-Jeghers [8]. Patients with hypogammaglobulinemia appear to have increased susceptibility to autoimmune disease. As might be expected with the frequent findings of gastric atrophy, achlorhydria, abnormal Schilling test results, and decreased gastrin secretion are also common in these patients. An increased incidence of pernicious anaemia has been noted. This may be related to the gastrointestinal tract disturbances that also occur. In addition patients have been found to have an increased frequency of various autoimmune disturbances: thyroid diseases, rheumatoid arthritis, eczematoid dermatitis, sarcoidosis and dermatomyositis. Hypogammaglobulinemia nodular lymphoid hyperplasia can be associated with amyloidosis. The pathogenesis of diarrhoea and the role of amyloidosis must be discussed. The infiltration of the intestinal wall with amyloid was evoked. Neoplasms are also common in patients with hypogammaglobulinemia. There is an increased incidence of gastric carcinoma [9]. Thymomas are frequently found, although fortunately many of these are benign. Patients with hypogammaglobulinemia also appear to be predisposed to lymphoreticular malignancies. The

effectiveness of corticosteroids was tested in common variable hypogammaglobulinemia. These drugs have been reported to decrease the diarrhoea and increase immunoglobulin synthesis. However, in some patients, high dose prednisone therapy resulted in decreasing the diarrhoea but not improving the immunoglobulin levels. Authors considered that the steroids might act by suppression of a postulated suppressor T-cell population present in some patients with this syndrome. This is unlikely since the administration of azathioprine did not alter the immunoglobulins or clinical status of patients. Whatever the mechanism, it seems to be systemic, since the locally acting oral bethamethasone-17-valerate, which has been shown to induce remission in patients with idiopathic steatorrhea, was ineffective [10].

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### CONCLUSION

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CVID is a heterogeneous group with antibody deficiency, accompanying immune dysregulation, T-cell deficiency, and poorly controlled inflammation leading to additional organ damage. Its cause remains unknown. It is important to consider hypogammaglobulinemia in any patient with a history of recurrent infections at different organ systems, and these patients should have a full assessment of immune system including measurement of serum immunoglobulin levels, IgG subclass levels, antibody function evaluation, and B and T-cell subset enumeration. Serum immunoglobulin levels are interpreted in relation to the normal range for age. Nodular lymphoid hyperplasia must be supervised with regular colonoscopy and biopsies to detect lymphoma. The considerable point was a mismatch primary clinical diagnosis of FAP, due to prominent polyp-like endoscopic appearance of the lesions throughout the digestive tract; though no dysplasia or adenomatous polyp was present. The large lymphoid follicles in the lamina propria of gut mucosa caused polypoid appearance leading to misdiagnosis.

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