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A case of long-undiagnosed Common Primary Immunodeficiency in adulthood

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Summary

Common Variable Immunodeficiency (CVID) is one of the most common causes of Primary Immunodeficiency Disorders (PIDs) and of Primary Hypogammaglobulinemia in adulthood. Clinical features include variable combinations of infectious diseases, autoimmune diseases, lymphoproliferative disorders and gastrointestinal diseases.

In this case report, delayed detection of the disease had a negative prognostic impact, despite prompt antibiotic and replacement therapy. The unfavourable prognosis was due to multi-organ failure (namely lungs, heart and liver) and to a number of chronic and acute infectious diseases.

Introduction

Clinical manifestations of immunodeficiency disorders (IDs) include the following: a) unusual medical condition (i.e. an infection which is unusual in respect to disease agent, complication, duration and severity); b) presence of non-infection-related symptoms, such as bronchiectasis with unknown cause, poor wound healing, chronic diarrhoea, malabsorption, premature loss of teeth, autoimmune disorders (especially when occurring in combination), hematologic disorders, failure to thrive, recurrent aphthous ulcers and, occasionally, c) family history (autosomal recessive disorders, x-linked disorders or clusters) (1).

The commonest IDs in adulthood include Secondary Immune Dysfunction and Primary Immunodeficiency Disorders (PIDs), such as IgA deficiency, Common Variable Immunodeficiency (CVID) and some complement deficiencies (1). The diagnosis of CVID is established by the following criteria: marked decrease in IgG levels (< 4.5 g / l for adults) and in the level of at least one of the IgM or IgA isotypes; onset at over 2 years of age; absence of isohemagglutinins and/or poor response to vaccines; other defined causes of hypogammaglobulinemia excluded (2,3).

In our case, delayed disease recognition negatively affected the patient's prognosis. The fatal outcome was ultimately due to progressive multi-organ failure and to multiple chronic and acute infectious diseases.

Case report

A 70-year-old male patient presented to our clinic in August 2011 with diarrhoea, loss of appetite, and increased waist circumference.

Detailed anamnesis revealed a history of Toxoplasmosis and Cytomegalovirus infection 20 years previously (only serolog-

ical markers had been tested for positivity: no DNA analysis had been carried out directly on the pathogens). The patient also reported multiple hospitalisations and outpatient visits for pneumonia (including necrotising pneumonia) and bronchitis, Chronic Obstructive Pulmonary Disease (COPD) with flare-up episodes associated with bronchiectasis, Secondary Chronic Pulmonary Heart Disease (NYHA III), Chronic Respiratory Failure and Permanent Atrial Fibrillation (AF) treated with anticoagulants. In two cases upon admission to hospital, bronchoalveolar lavage and sputum tested positive for Pseudomonas aeruginosa, Atypical mycobacteria, and Haemophylus. Family history for immune deficiencies was negative.

In 1994, the patient underwent medical examinations for moderate leukopenia, severe hypogammaglobulinemia and recurrent respiratory infections. US abdomen, bone marrow aspiration and biopsy were negative. Flow cytometry analysis of peripheral blood lymphocyte subsets showed mild CD4+ lymphocyte depletion (Total CD3 T lymphocytes: 87%, range: 70-80; CD 19 B lymphocytes: 5%, range: 5-15; CD4 T lymphocytes: 25%, range: 35-55; CD8 T lymphocytes: 67%, range: 20-35%).

In August 2008, the patient had episodes of diarrhoea, which resolved spontaneously after 10 days. Colonoscopy was negative in this case. In June 2011, the subject was treated unsuccessfully with metronidazole for persistent diarrhoea and fever secondary to Giardia lamblia infection. Upon observation, he showed cachexia, rhonchi, basilar crackles, and AF (rate: 78 bpm).

On to hospital admission, laboratory tests revealed the following: mild microcytic anemia (Hb 13.1 g/dl, MCV 65 fl), normal white blood cell and platelet counts (PLT 271000/mmc, WBC 8190/mmc, N 4360/mmc, L 3030/mmc, M 740/mmc, E 50/mmc, B 10/mmc), high prothrombin time (PT 3.67), hypokalemia (2.7 mM/l), cholestasis (ALP U/l 237 vs. 129 U/l, GammaGT 82 U/l vs. 61 U/l), moderate inflammatory syndrome (CRP 34.8 mg l vs. 5 mg/ll), low protein levels (48 g/l vs. 60 g/l), and Giardia lamblia in stools.

The manifestations requiring medical attentions were in our view: cachexia, chronic diarrhoea secondary to Giardia lamblia infection, recurrent respiratory infections associated with hepatomegaly, splenomegaly, ascites, cholestasis, and altered coagulation. We formulated two diagnostic hypothesis: a) immunodeficiency secondary to liver cirrhosis, lymphoproliferative disorder or viral infection (HIV); or b) primary immune deficiency with splenomegaly.

Immunodeficiency tests revealed severe hypogammaglobulinemia (gamma globulin: 2.4%, range: 11.1-18.8). Immunoglobulin values were of particular interest: IgA < 0.05 g/l (range: 0.7-4); IgG 0.72 g/l (range: 7-16); IgM 0.09 g/l (range: 0.4-2.3), tests were negative for both Bence Jones protein and alkaline phosphatase bone isoenzyme. Analysis of peripheral blood lymphocyte subsets showed: Total CD3 T lymphocytes: 92%, range: 70-80; CD19 B lymphocytes: 3% [90/mmc], range: 5-15; CD4 T lymphocytes: 8 % [242/mmc], range: 35-55; CD8 T lymphocytes: 79% [2394/mmc], range: 20-35; CD4/CD8 ratio 0.1, range: 0.8/5; NK lymphocytes: 6%, range: 8-22%. Both ELISA and p24 antigen test were negative for HIV.

The clinical scenario now changed to humoral immune and lymphocyte deficiency (predominantly B-cells CD19+ and T-cells CD4+) associated with hepatosplenomegaly. Taking into account the patient's age, we formulated the following two diagnostic hypothesis: a) primary immunodeficiency (CVID); and b) immune deficiency secondary to lymphoproliferative disease, drug intake (especially corticosteroids), or excess loss (nephrotic syndrome, exudative enteropathy, skin loss).

The patient underwent additional laboratory analyses. Complement C3 and C4 levels were within normal limits, while chest X-ray and chest-abdomen CT showed bronchiectasis with bibasal mucus, paratracheal adenopathy (1.2 cm diameter), chronic liver disease with caudate and left lobe hypertrophy, ascites, and enlarged, inhomogeneous spleen (**figure 1**). Bone marrow aspiration identified inadequate erythroid maturation, whereas bone marrow biopsy showed maturing trilineage hematopoiesis, moderate CD8+T lymphocytosis, and significant reduction of plasma cells. Abdominal US revealed liver with nodular cirrhosis, portal vein ectasia, splenomegaly (14,1 cm) and moderate ascites (**figure 2**). Qualitative viral load tests for HCV RNA and quantitative HBV DNA assays were negative, as determined by real-time PCR. Antibody-specific serological assays were also negative (ANA, AMA, ASMA, LKM: IFI test; minor hepatotropic viruses: PCR for CMV e EBV DNA). Paracentesis showed ascitic fluid lymphocytosis (4L evacuation: 425/µl WBC, 21% neutrophils, 70% lymphocytes, 1% eosinophils).

To rule out peritoneal TBC we planned a laparoscopic peritoneal biopsy, followed by EGDS. Quantiferon was negative, while gastroscopy showed duodenal ulcer and biopsies were negative for lymphoma (MALToma). Based on laboratory tests results, we diagnosed CVID (Common Variable Immunodeficiency). The patient was put on immunoglobulin replacement therapy (0.5 g/Kg) administered monthly in a day-hospital regimen.

From February to March 2012, the patient was again admitted to our department for hemorrhagic shock following paracentesis. He also presented left pneumonia, with sputum testing positive for Pseudomonas aeruginosa, and reported a new episode of diarrhoea. At analysis, stool specimens were strongly positive for Giardia lamblia. Pneumonia was treated with cephalosporin and peritoneal biopsy was suspended due to the patient's overall clinical condition.

On a subsequent admission to hospital, from April to May 2012, the patient showed the following:

- Watery diarrhoea with stools testing positive for Giardia lamblia (subject to therapy with metronidazole 250 mg x 3 followed by albendazole 400 mg x 3) and for Clostridium difficile (remission 1 month from the start of therapy with oral vancomycin).
- Persistent left pneumonia with sputum testing positive for several types of bacteria (namely, Corynebacterium striatum, Stenotrophomonas maltophila and Pseudomonas aeruginosa).

Based on antibiogram results, the patient was intravenously injected with ceftazidime and levofloxacin, showing signs of clinical improvement. However, persistent radiographic infiltrates were also detected.
In November 2012, the patient presented again to our department with the following symptoms:

- Severe weight loss and cachexia;
- Dyspnea, cough, global respiratory failure. Chest X-ray showed bilateral edema, disatelectatic zones, apical fibrosis and infiltrates in the right upper pulmonary lobe. Bronchoalveolar lavage was positive for multidrug-resistant Pseudomonas aeruginosa and S. Aureus, while sputum was positive for acid-alcohol resistant bacilli (negative BK PCR).
- Diarrhoea with negative stool specimens;
- AF with high ventricular response.

The patient was kept in isolation and treated with high-flow oxygen, diuretics and antibiotics (imipenem 550 mg x 4 and levofloxacin750 mg, injected intravenously).
Death occurred in November 2012 from acute pulmonary edema.

Discussion

Incidence of CVID is estimated between 1:10.000 and 1:50.000. The age of onset is usually in the second or third decade of life (3).
At a first glance, there appeared to be an obvious mismatch between our patient's age and diagnosis of CVID. However, a review of the literature suggests that CVID can indeed occur at any age (4). The French DEFI study group also identified a subset of CVID, referred to as 'late onset combined immunodeficiency' (LOCID), characterised by clinically relevant T-cell insufficiency and accounting for approximately 8.9% of CVID cases. The inclusion criteria set by the DEFI group were: CD4+ T cells below 200/µl and evidence of opportunistic infections (4-6).
In the present case, a history of Cytomegalovirus and Toxoplasma gondii infection and the absence of common clinical manifestations of LOCID at the time of hospitalisation, such as lymphopenia in bone marrow biopsies and in the blood stream, and absence of sarcoid-like granulomas (included pulmonary granulomas), argued against this diagnosis. The presence of Cytomegalovirus and Toxoplasma gondii infection was determined on the basis of serological positivity alone, as the DNA of those pathogens had not been tested.
The patient's clinical history was characterised by progressive decline secondary to recurrent respiratory infections and by abnormal findings in the digestive tract and liver. As reported in the literature, the clinical phenotype is heterogeneous and includes (2,7,8,9) (**table 1**):

- infectious diseases (over 90% of CVID patients had bacterial pathogens in the upper and lower airways and in the gastrointestinal tract) (2);
- autoimmune diseases (accounting for 20% of CVID cases);
- lymphoproliferative disorders and gastric cancer (approximately 40-50% of CVID cases, possibly due to carcinogenic pathogens such as Helicobacter pylori and Epstein Barr virus, or to impaired tumour cell surveillance);
- gastrointestinal symptoms: enteritis (Giardia lamblia, Salmonella, Campylobacter), both non-bloody (sprue-like) and bloody (chronic inflammatory bowel disease) diarrhoea, asymptomatic or unformed stools (nodular lymphoid hyperplasia of the duodenum and ileum), cholestasis (nodular regenerative hyperplasia or granulomatous hepatitis with portal hypertension);
- rarely absent complications.

In our case, the unfavourable course could most likely be ascribed to chronic, non-infectious complications. In literature, the prognosis for CVID is seen as depending on a number of causes, ranging from bronchiectasis, to enteropathy and autoimmunity and from B cell percentage to Ig and T cell response (9, 10). Interestingly, the risk of death is also 11 times higher for patients with non-infectious complications (lymphoma, chronic hepatitis, structural lung disease and chronic gastrointestinal disease) (7-10).
A delayed diagnosis (from 1994 to 2011) was in the present case a negative prognostic factor. Indeed, several studies document that age at diagnosis has a significant impact on the outcome of the disease (7). The existing literature also suggests that Ig therapy (administered either intravenously or subcutaneously) reduces the recurrence of infections, delays the onset of pulmonary complications (such as bronchiectasis and respiratory failure), and allows early detection of other complications (especially lymphomas and solid tumours) by approximately 10% (9,10).
In conclusion, taking into account the patient's history, as well as any signs and symptoms of recurrent infections, is of critical importance for a successful management of the disease. Specifically, primary immunodeficiencies, most notably CVID, cannot be ruled out in adulthood, particularly when unusual infections (or unusual infection manifestations) should occur.

Table 1 *- Clinical phenotype in CVID (9, modified).*

Infections
Respiratory Tract Infections • Recurrent sinusitis, otitis, bronchitis • Pneumonia (encapsulated bacteria, rare opportunistic infections due to cellular immunodeficiency: Pneumocystis, HSV, CMV, Candida albicans, Mycobacterium)
Digestive Tract Infections • Giardia lamblia, Salmonella, Campylobacter enteritis
Meninges, Skin and Mucosa, Joints Meningitis, Herpes zoster, oligoarthritis due to Mycoplasma infection, Papillomavirus infection
Abnormal findings in the liver and the digestive tract • Non-bloody diarrhoea associated with a sprue-like disease (villous atrophy, pernicious anaemia, sprue-like malabsorption) and bloody diarrhoea resulting from chronic inflammatory bowel disease (Crohn-like disease) • Nodular lymphoid hyperplasia in the duodenum and ileum (either asymptomatic or associated with unformed stools) • Nodular regenerative hyperplasia of the liver tissue, or seronegative granulomatous hepatitis. Usually, liver function in CVID patients is preserved but portal hypertension may develop • Viral hepatitis (seronegative hepatitis B and C as well as Cytomegalovirus or Epstein Barr virus hepatitis should be ruled out by searching for hepatitis antigen or viral RNA, respectively)
Nodal and extranodal lymphoproliferative disorders • Lymphoid hyperplasia (primarily of the lymph nodes and spleen) • Lymphoma (extranodal diffuse large B-cell lymphoma or Hodgkin lymphoma, often associated with EBV, MALTomi) • Granulomatosis • Nodular lymphoid hyperplasia of the gastrointestinal tract
Granulomatous lesion • Granulomatous interstitial lung disease with poorer prognosis • Granulomatous disease similar to sarcoidosis (lung and lymph nodes; also liver, skin, spleen, bone marrow, gastrointestinal tract, brain and kidney, in decreasing frequency)
Autoimmunity • Thrombocytopenia (Thrombotic Thrombocytopenic Purpura (TTP)) • Autoimmune haemolytic anaemia • Autoimmune neutropenia and autoimmune cytopenia • Less frequently: autoimmune thyroid disease, primary biliary cirrhosis, autoimmune hepatitis, vitiligo, pernicious anaemia, psoriasis, rheumatoid arthritis and systemic lupus erythematosus
Dermatologic manifestations • Alopecia, non-necrotizing granulomas

Figure 1 *- US abdomen of patient: splenomegaly.*

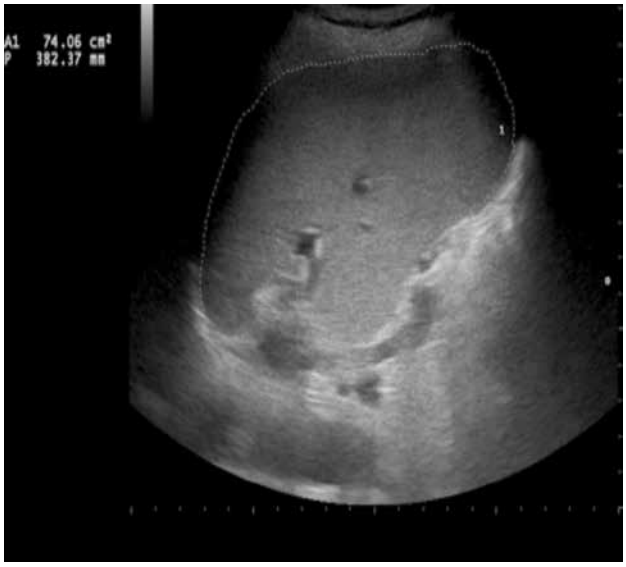
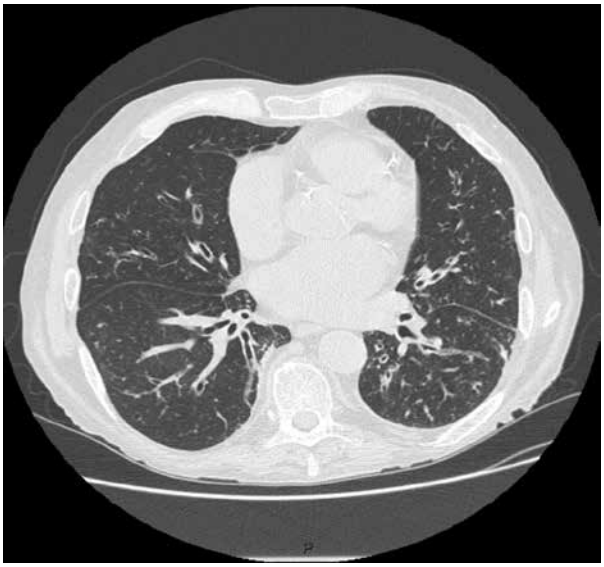


Figure 2 *- Chest CT of patient.*



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