Clinical Case Report

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Primary intestinal lymphangiectasia in an elderly female patient

A case report on a rare cause of secondary immunodeficiency

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Abstract

Protein loss via the gut can be caused by a number of gastrointestinal disorders, among which intestinal lymphangiectasia has been described to not only lead to a loss of proteins but also to a loss of lymphocytes, resembling secondary immunodeficiency. We are reporting on a 75-year-old female patient who came to our hospital because of a minor stroke. She had no history of serious infections. During the diagnostic work-up, we detected an apparent immunodeficiency syndrome associated with primary intestinal lymphangiectasia. Trying to characterize the alterations of the immune system, we not only found hypogammaglobulinemia and lymphopenia primarily affecting CD4+, and also CD8+ T cells, but also marked hypocomplementemia affecting levels of complement C4, C2, and C3. The loss of components of the immune system most likely was due to a chronic loss of immune cells and proteins via the intestinal lymphangiectasia, with levels of complement components following the pattern of protein electrophoresis. Thus, intestinal lymphangiectasia should not only be considered as a potential cause of secondary immune defects in an elderly patient, but can also be associated with additional hypocomplementemia.

Abbreviations: ACE = angiotensin-converting enzyme, ANA = antinuclear antibodies, ANCA = antineutrophil cytoplasmic autoantibodies, BSR = blood sinking reaction, CHAPLE = CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, protein-losing enteropathy syndrome, CRP = C-reactive protein, CT = computed tomography, EBV = Ebstein-Barr virus, HIV = human immunodeficiency virus, IPMN = intraductal papillary mucinous neoplasm, MRCP = magnetic resonance cholangiopancreaticography, PIL = primary intestinal lymphangiectasia.

Keywords: hypocomplementemia, intestinal lymphangiectasia, secondary immunodeficiency

1. Introduction

Secondary immunodeficiency can result from a variety of underlying disease states and environmental exposures including infections, immunosuppressive agents, and malignancies. More rarely, secondary immunodeficiency is the consequence of disorders leading to protein loss such as severe dermatitis, nephrotic syndrome, and protein-losing enteropathies. Protein loss via the gut can be caused by a number of gastrointestinal disorders, among which intestinal lymphangiectasia has been described to not only lead to a loss of proteins but also to a loss of lymphocytes, resembling a sort of combined immunodeficiency.[1,2] However, despite the suspected loss of proteins, low levels of complement components in patients with primary intestinal lymphangiectasia (PIL) have only been described in the context of additional atypical hemolytic uremic syndrome[3,4] or deficiency of CD55 (complement decay accelerating factor).[5] Here we describe and characterize the rare case of an elderly patient who was diagnosed to have PIL being associated with hypogammaglobulinemia and T-cell lymphopenia. In addition, our patient had marked hypocomplementemia in the absence of signs of complement-mediated disease, suggesting that the lymphatic loss of components of the immune system in patients with PIL can include complement molecules.

2. Case report

A 75-year-old woman, suffering from Parkinson disease, was admitted to our hospital because of a minor stroke. She had a 1-month history of inappetence, confusion, disorientation, and depression. In addition, she described a variable weight loss despite regular food intake. She did not refer to any symptoms that were suggestive for an inflammatory disease. Particularly, she did not have any gastrointestinal symptom such as diarrhea, abdominal pain, or vomitus. She also did not report any particular risk factor such as smoking or excessive alcohol consumption, and there was no history of severe infections in the past.

In the clinical examination, we found a bilateral lymphedema of the legs. Otherwise, the patient had a slim stature with no other

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Table 1

Blood count and protein electrophoresis.

	Patient (day 1)	Normal range
Hemoglobin	135 g/L	120–160 g/L
Thrombocytes	140×0^9/L	$150–450 \times 10^9$/L
Leukocytes	4.52×10^9/L	$3.50–10.00 \times 10^9$/L
Lymphocytes	0.651×10^9/L	$0.9–3.3 \times 10^9$/L
Neutrophil granulocytes	3.286×10^9/L	$1.300–6.700 \times 10^9$/L
Total protein	38.0 g/L	62.0–80.0 g/L
Albumin	18.8 g/L	35.0–53.0 g/L
Alpha globulins		
Alpha-1	2.5 g/L	1.9–3.9 g/L
Alpha-2	8.9 g/L	4.5–9.0 g/L
Beta globulins		
Beta-1	2.8 g/L	3.2–5.5 g/L
Beta-2	1.7 g/L	2.2–5.0 g/L
Gamma globulins	3.4 g/L	5.6–15.0 g/L

relevant findings apart from the well-known neurological signs related to her Parkinson disease.

In the laboratory work-up, inflammatory markers such as C-reactive protein (CRP), blood sedimentation rate (BSR), and total white blood cell count were normal. In the differential leukocyte count, there was no conspiciuous cell population reported. However, we observed severe hypoalbuminemia and also lymphocytopenia (Table 1).

2.1. Diagnostic work-up

Our first differential diagnosis included malignant (solid or hematological), infectious, and autoimmune disorders. In an abdomino-thoracic computed tomography (CT) scan, we did not find any significantly enlarged lymph nodes or signs of any solid tumor, neither in the area of the chest nor abdomen. The only finding was a slightly prominent duodenal papilla. Consequently, an upper endoscopy including the proximal jejunum was performed. There, diffusely spread jejunal lymphangiectasias were found, whereas the region of the papilla was unremarkable (Fig. 1A and B).

Histologically, the presence of lymphangiectasia was confirmed (Fig. 1C and D). An endoluminal ultrasound and a magnetic resonance cholangiopancreaticography (MRCP) did not show any evidence of a pancreatic tumor, apart from tiny cystic lesions connected with the main duct (maximal diameter 16 mm) that were assessed as intraductal papillary mucinous neoplasm (IPMN) of the branch duct type. In the duodenal biopsies, there was no evidence of tropheryma whipplei infection, celiac disease, or other types of inflammatory disease. A colonoscopy could exclude significant pathology. In addition to this, a serological testing for antitransglutaminase IgA antibodies in the absence of IgA deficiency was negative. Standard stool cultures came out to be negative, and a fecal calprotectin test showed no increase suggestive of intestinal inflammatory activity. Therefore, the diagnosis of PIL was established.

To assess the possibility of an underlying and/or accompanying autoimmune/autoinflammatory disease, we determined a panel of serum markers such as antineutrophil cytoplasmic autoantibodies (ANCAs), antinuclear antibodies (ANAs), anti-double stranded DNA antibodies, complement components, cryoglobulins, and also an immune electrophoresis, serum angiotensin-converting enzyme (ACE), total IgG, IgM, and IgA. The screening for cryoglobulins, ANCAs, and ANAs came out to be negative, and the serum ACE level was normal. However, in the absence of a paraprotein, we saw a reduced fraction of albumin and gammaglobulins, and to a much lesser extent a reduction of the beta-fractions, whereas the alpha-fractions were not diminished

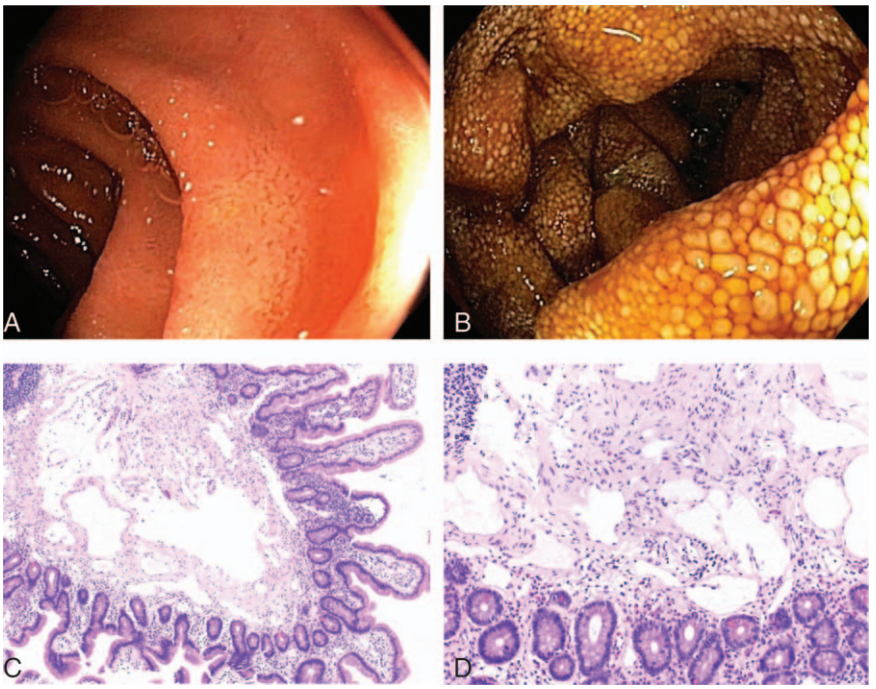

Figure 1. Endoscopic view on normal duodenum (A) and the proximal jejunum (B) showing flattened villae as typical feature of gastrointestinal lymphangiectasia (by courtesy of Professor Degen, University Hospital Basel). Jejunal biopsy revealed marked submucosal lymphangiectasia. Hematoxylin and eosin (H&E) staining. Magnification 100× (C) and 200× (D), respectively.

Table 2

Serum immunoglobulin concentrations, levels of complement components, and peripheral blood lymphocyte counts.

	Patient	Normal range
IgG	**2.3 g/L**	7.0–16.0 g/L
IgA	0.79 g/L	0.70–3.80 g/L
IgM	2.43 g/L	0.50–2.60 g/L
CH50	**44 U/mL**	70–180 U/mL
Complement C1q	0.10 g/L	0.10–0.25 g/L
C1 inhibitor	0.39 g/L	0.21–0.39 g/L
Complement C4	**0.07 g/L**	0.1–0.4 g/L
Complement C2	**0.010 g/L**	0.014–0.025 g/L
Complement C3c	**0.079 g/L**	0.8–1.8 g/L
Lymphocytes absolute	0.535×10^9/L	$0.900–3.300 \times 10^9$/L
CD3+	**197/μL**	742–2750 cells/μL
CD3+/CD4+	**123/μL**	404–1612 cells/μL
CD3+/CD8+	**64/μl**	220–1129 cells/μl
CD19+	301/μl	80–616 cells/μl
CD3−/CD16+/CD56+	109/μl	84–724 cells/μl

Values below the lower limit of the normal range have been highlighted as bold values.

(Table 1). With regard to levels of immunoglobulins and complement components, we found a significantly decreased level of gammaglobulins (IgG), and also hypocomplementemia affecting at least C4, C2, and C3, and, to a lower extent, C1q, but not C1 inhibitor (Table 2). Hyocomplementemia could be confirmed at several time points and by 2 different routine laboratories. The loss of specific components of the complement system went in parallel with the reduced electrophoretic protein concentrations that were measured (Fig. 2).

Because there was relevant lymphopenia, we also tested the patient for HIV, which was found to be negative. As mentioned, the patient did not have any clinical signs of an active viral infection (more specifically, there were no erythema, splenomegaly, lymphadenopathy, fever, rhinitis, or pharyngitis). Further serological testing showed immunity to Ebstein-Barr virus (EBV) and toxoplasmosis, but was negative for syphillis, *Borrelia burgdorferi*, tick-borne encephalitis virus, *Trichinosis*, *Rickettsiae*, and *Leptospirosis*.

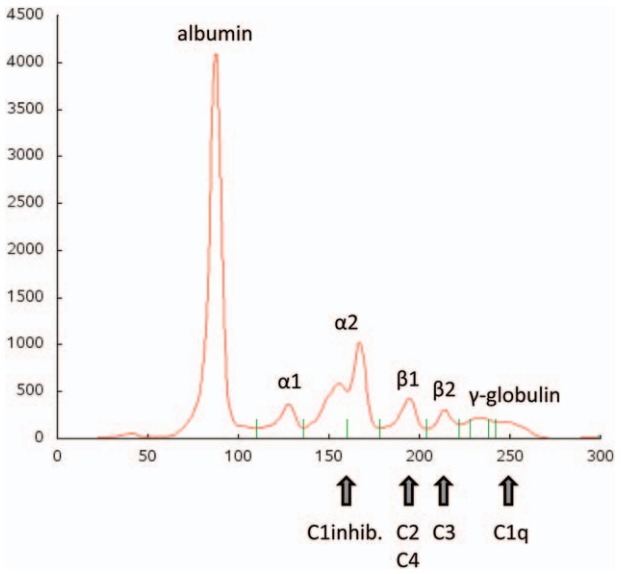

Figure 2. Protein electrophoresis with assumed position of complement components.

To characterize the lymphocytopenia, a phenotyping of the peripheral blood mononuclear cells was performed. Interestingly, we found that the lymphocytopenia was restricted to CD4+ and CD8+ T cells, whereas B lymphocytes and natural killer (NK) cells were within the normal range (Table 2).

The patient was discharged for neurorehabilitation without specific treatment for her apparent immunodeficiency. Twelve months after discharge, she still reported on edema of the lower legs, but there was no clinical sign suggestive of a malignant or inflammatory disease.

2.2. Ethics approval and consent to participate

The patient in this case report provided informed written consent before the use of her data. The consent was approved by the Ethical Committee of Northwest Switzerland (EKNZ).

3. Discussion

We are reporting on a case of an elderly female patient who showed significant lymphopenia and hypoalbuminemia, together with bilateral lymphatic edema of the lower extremities. She not only had accompanying hypogammaglobulinemia but also marked hypocomplementemia. The diagnostic work-up revealed an intestinal lymphangiectasia that was considered to be primary due to the absence of a tumorous lesion of the gastrointestinal tract and other chronic inflammatory diseases such as Whipple, Crohn, and celiac disease.

Primary intestinal lymphangiectasia (Waldman disease) seems to be a rare disorder and normally is diagnosed early in life. PIL has classically been reported as a syndrome with edema of the lower extremities and a protein-loosing enteropathy accompanied by hypoproteinemia and often diarrhea.[1] It most frequently has been described in children, and our patient is among the oldest with PIL reported thus far.[2,6,7] However, our observation is well in line with more recent reports suggesting that the prevalence of intestinal lymphangiectasia might be underestimated and that the classical syndrome is only 1 end of the clinical spectrum.[8,9] The majority of intestinal lymphangiectasia might have a benign prognosis and therefore might be diagnosed only late in life (if ever). Due to the intestinal loss, our patient had a striking hypoalbuminemia, which, on the first view, explained the overall level of hypoproteinemia. However, in the protein electrophoresis, it became clear that the protein loss was not limited to albumin, but showed a pattern suggestive of a differentiated loss: whereas the alpha-1 (including high-density lipoprotein [HDL]) and alpha-2 fraction (including antithrombin III and C1 inhibitor) were quantitatively normal, the beta-1 (including transferrin, and also complement C4 and C2) and beta-2 fraction (including complement C3) were slightly decreased. Finally, the gamma-globulin fraction showed the strongest reduction and was also associated with depletion of complement C1q.

Trying to better characterize the components of the immune system being affected by intestinal lymphangiectasia, we found that total IgG was strongly diminished, whereas IgM and IgA were normal. To the best of our knowledge, the marked hypocomplementemia in our patient is the first being reported in a patient with PIL in the absence of additional atypical hemolytic syndrome or signs of complement-mediated disease including CHAPLE (CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, protein-losing enteropathy) syndrome.[3–5,10] Since low complement levels followed the

protein electrophoretic pattern and affected several molecules being part of different activation pathways of the cascade, it is likely that hypocomplementemia, as observed in our patient, was part of the relatively broad spectrum of proteins being lost via intestinal lymphangiectasia rather than due to genetic variations. Thus, we suspect that hypocomplementemia might be a more frequent phenomenon in patients with PIL as previous case descriptions rarely report on complement levels. However, we cannot exclude a genetic variant of a complement component as primary trigger of intestinal lymphangiectasia in our patient or even a combination of both mechanisms.

In addition to hypogammaglobulinemia and hypocomplementemia, the immunophenotyping of peripheral blood lymphocytes revealed an impressive loss of CD4+ and CD8+ T cells, whereas NK cells, and also B lymphocytes were not affected. This observation is well in line with previous reports,[11,12] suggesting that low T-cell numbers in PIL patients are probably not only due to simple enteric loss, but also the consequence of an altered activation of residual T cells (leading to death) and an insufficient compensatory thymic production.

Thus, our patient had apparent secondary immunodeficiency primarily affecting T lymphocytes, total IgG, and complement components. However, a major question in the context of this striking depletion of components of the peripheral blood immune system is its clinical relevance. Despite the impressive laboratory findings, the lack of lymphocytes, IgG, and complement components seems not to have caused immunodeficiency as defined by recurrent severe infections. This is in line with previous reports of PIL in which severe infections have not been described to be a dominant clinical feature.[1,13] We assume that in this setting, tissue-based components of the immune system might still be intact and provide sufficient protection, which also raises the more general question of how well peripheral blood measurements allow a judgment on overall immune functions.

Another question that arose during the diagnostic procedure was whether there was any acute inflammation that might have been missed by the conventional diagnostic approach. As the beta-fractions showed a minor decrease, it might have been possible that this decrease also led to falsely low CRP levels including other positive acute-phase proteins, whereas negative acute-phase proteins such as transferrin or complement C3 indeed were diminished. However, the patient had no fever or other clinical signs of inflammation during hospitalization and the following months.

4. Conclusions

In conclusion, PIL can lead to a combined defect in immunoglobulins and peripheral blood T cells that can be associated with additional hypocomplementemia. Although being a rare clinical entity in adults it might be underdiagnosed and therefore needs to be considered as an underlying cause during the diagnostic work-up of patients with apparent immunodeficiency, even in an elderly patient.

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