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CASE REPORT

Revisiting protein-losing enteropathy: a rare case of chorea*

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Introduction

Protein-losing enteropathy is an umbrella term for a diverse group of disorders causing uncompensated plasma protein loss into the gastrointestinal tract in the absence of kidney or liver disease. In a healthy individual, protein loss through the gastrointestinal tract is about 10% of the normal turnover.[1] Most plasma proteins in the gastrointestinal tract are broken down into amino acids and reabsorbed. The liver can compensate for excessive protein loss by increasing its production by up to 2.7 times.[2] As soon as protein loss exceeds liver production, signs of protein-losing enteropathy develop. The molecular weight does not influence which proteins are lost; however, proteins with longer half-lives are most affected, whereas those with a rapid turnover are less affected.[3] Depending on the cause, patients may also experience malabsorption of other compounds (e.g. fat and fat-soluble vitamins).

There are three mechanisms whereby protein-losing enteropathy can occur. The first is caused by erosive damage to the mucosa, resulting in an exudative loss, as seen in inflammatory bowel disease or gastrointestinal malignancy. The second is increased permeability of the mucosa without erosions, examples being coeliac disease or connective tissue disorders. The third mechanism is lymphatic obstruction, which can have either congenital or acquired causes.

The clinical presentation is highly variable and depends on the underlying cause and the subsequent complications that may develop. Patients may complain of diarrhoea, abdominal pain, cramps, bloating, or flatulence. Most will have peripheral oedema, pitting if from hypoalbuminaemia, or non-pitting if from lymphatic obstruction. Pericardial effusion, pleural effusion, or ascites may also be present.

The diagnosis of protein-losing enteropathy should be suspected if no other cause for the low plasma proteins is found, such as inadequate intake, inadequate synthesis, or excessive renal loss. Classically, the proteins most affected are albumin, gamma globulins, fibrinogen, transferrin, and ceruloplasmin. There may also be fat-soluble vitamin deficiencies. The preferred method for confirming the diagnosis is alpha-1 antitrypsin clearance; however, scintigraphy can also be used. Alpha-1 antitrypsin is resistant to proteolysis in the intestinal lumen and is, therefore, excreted intact in the stool.[4] The alpha-1 antitrypsin clearance increases with diarrhoea and intestinal bleeding, which may lead to false positives.[5] After protein-losing enteropathy has been confirmed, further investigation should focus on the cause, guided by history and physical examination. This may include further imaging, endoscopy, or specific laboratory testing.

Case description

A 16-year-old female presented to our hospital with a four-day history of involuntary choreiform movement of all four of her limbs. She reported chronic diarrhoea and passing loose stools three times a day for years, to which she had become accustomed. Clinically, she had no oedema.

Hospital records revealed that she was previously diagnosed with rheumatic heart disease and protein-losing enteropathy. The cause of the protein-losing enteropathy was attributed to lymphatic obstruction from disseminated tuberculosis when she was four years old; however, it was never confirmed by alpha-1 antitrypsin clearance or scintigraphy. She had persistently low plasma proteins, albumin, immunoglobulin G (IgG) levels, and deficiencies in vitamins D and E. She was unfortunately lost to follow-up for a year until this presentation.

She was taking antibiotic prophylaxis for her rheumatic heart disease but defaulted on this treatment, leading to the initial suspicion of acute rheumatic fever. Using the Jones criteria, the one major criterion met was Sydenham's chorea, and the two minor criteria met were raised inflammatory markers and a history of fever. Other criteria were excluded on clinical examination, electrocardiogram, and echocardiogram. She was admitted to the hospital and empirically started treatment for acute rheumatic fever. Levetiracetam, clonazepam, and risperidone were prescribed for the chorea. Her antistreptolysin O titre proved negative.

Upon further testing, she still had low levels of total protein (37 g/L), albumin (8 g/L), IgG (6.82 g/L), and vitamin D (27.6 nmol/L). Kidney and liver functions were normal. She also had hypocalcaemia with an ionized calcium of 0.77 mmol/L, with

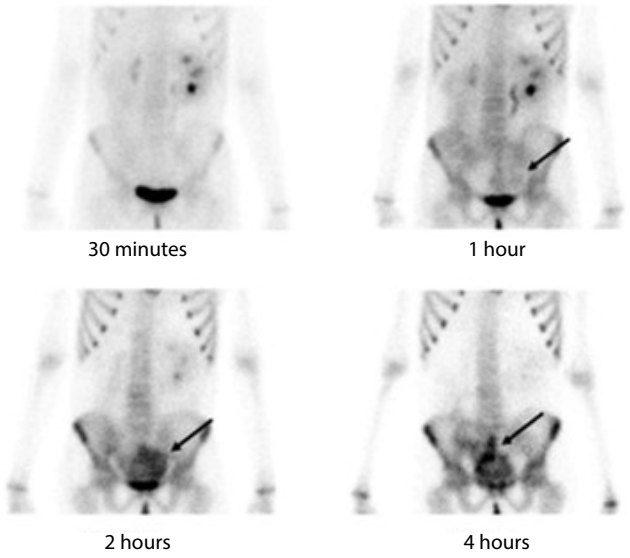

Figure 1: Technetium 99m-methylene diphosphonate static images of the abdomen at various time points

normal parathyroid and thyroid levels. Calcium and vitamin D supplementation was commenced.

To confirm the diagnosis of protein-losing enteropathy, we performed both an alpha-1 antitrypsin clearance and scintigraphy. Using the tracer technetium 99m-methylene diphosphonate (^{99m}Tc-MDP), scintigraphy showed radiopharmaceutical accumulation in the bowel, originating in the terminal ileum region (Figures 1 and 2). The images were in keeping with the previous diagnosis of lymphatic obstruction in the terminal ileum due to the disseminated tuberculosis infection. The alpha-1 antitrypsin clearance was 81 ml/day, consistent with protein-losing enteropathy.

In further investigations, we performed a bidirectional endoscopy that showed nodular atrophic duodenitis with marked scalloping and distortion of the duodenal architecture (Figure 3). A diffusely

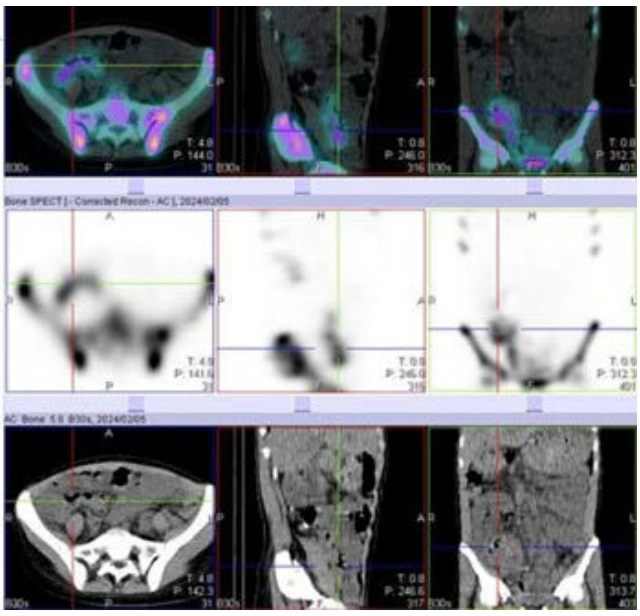

Figure 2: Four-hour SPECT/CT

Figure 3: Second part of the duodenum during upper endoscopy

oedematous bowel wall was noted on the lower endoscopy. The histology revealed xanthomas of the duodenum and chronic active colitis of the colon. Serological screening for coeliac disease proved negative, with normal immunoglobulin A (IgA) levels. The patient's brain magnetic resonance imaging (MRI) was normal, and her chorea improved following the neuropathic therapy and the calcium and vitamin D supplementation.

A working diagnosis of inflammatory bowel disease was made, and she was started on sulfasalazine. A diet high in protein, low in fat, and high in medium-chain triglyceride was employed. At follow-up, the patient reported resolution of the diarrhoea and her albumin level had increased.

Discussion

Our patient had the atypical presentation of chorea, which is possibly due to hypocalcaemia and vitamin D deficiency resulting from fat-soluble vitamin malabsorption. A previous case report of a paediatric patient with protein-losing enteropathy, hypocalcaemia, and vitamin D deficiency who developed hemichorea demonstrated resolution after supplementation, similar to our case.[6] Acute rheumatic fever was less likely as the Jones criteria were not met, and the patient responded favourably to other treatments. The management of protein-losing enteropathy is directed at the underlying cause and dietary repletion. A diet high in protein, low in fat, and high in medium-chain triglycerides is advised.[7]

We used both alpha-1 antitrypsin clearance and ^{99m}Tc-MDP imaging to confirm the diagnosis of protein-losing enteropathy, with the latter being more accessible at our hospital. The 24-hour stool specimen collection was also cumbersome for the patient. The preferred nuclear medicine studies are ^{51}Cr-labeled albumin or ^{125}I-labelled albumin.[8] These tracers are expensive, not readily available at our facility, and have the drawback of not localising the site of protein loss, as they are not imaging radiotracers. We used ^{99m}Tc-MDP, a bone-seeking agent that does not usually

appear in the gastrointestinal tract. False positives from a ^{99m}Tc-MDP study can be due to stomach uptake of free technetium. However, with our scan, the 30-minute neck static scan showed no uptake in the thyroid or stomach, thus excluding a false positive result. There have only been a few case reports of ^{99m}Tc-MDP being used in the diagnosis of protein-losing enteropathy.

Finally, our case emphasises the importance of bidirectional endoscopy in the further investigation of patients with protein-losing enteropathy. With the macroscopic appearance of the duodenum, other diagnoses were considered, for example, Whipple's disease or *Mycobacterium avium-intracellulare* infection. However, the patient's clinical improvement made these unlikely.

Conclusion

Protein-losing enteropathy has a wide range of clinical presentations, depending on its underlying cause and complications. In our case, it appears that the malabsorption of calcium and vitamin D led to the chorea. The recommendation is to confirm protein-losing enteropathy with an alpha-1 antitrypsin clearance test. Moreover, we found scintigraphy, specifically the use of ^{99m}Tc-MDP, a tracer usually used for bone scans, to be valuable. In the pursuit of finding an underlying cause, our case also affirms that bidirectional endoscopy is mandatory in the investigation of protein-losing enteropathy.

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