An unusual cause of eosinophilic pleural effusion and migrating biliary stenosis: *Strongyloides stercoralis* infection in a young immunocompetent man

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Abstract

We present the case of a 33 year-old Italian man who came to our attention for epigastralgia associated with polyserositis (pleural and pericardial and peritoneal effusion with the involvement of the Douglas excavation), in the absence of a significant medical history. Laboratory analysis revealed exudative eosinophilic pleural effusion; serial imaging techniques showed a transient stenosis of the right hepatic duct and a subsequent stenosis of the left hepatic duct. After several negative serological investigations, a positive anti-strongyloides IgG antibodies titre rose suspicions of Strongyloides infection, which was confirmed by positive stool sample for parasite. Ivermectin-therapy was started and the patient’s fully recovered.

Introduction

Strongyloides is a parasite that lives in the soil of rural areas of tropical and subtropical regions and occurs sporadically in temperate areas. Literature reports several cases of Strongyloides infection in immunosuppressed patients predominantly, with malignancies (especially haematological), autoimmune history, malnutrition, or with a history of alcohol abuse and cirrhosis or of travels in endemic countries. A prompt treatment with ivermectin can lead to a rapid resolution of a potentially lethal infection.

Case Report

A 33-year-old man, with modest smoking habit (1 pk/y), works in a waste disposal site (sewage sludge), lives in the countryside, owns hens, and consumes field herbs and rarely raw crustaceans. No significant past medical history is reported, except for a right knee arthroscopy in 1998. He has a family history of diabetes, and he does not take any medicine.
Before to come to our attention, he ran some diagnostic test for a persistent diarrhoea. Haematological screening for celiac disease, abdominal ultrasound and colonoscopy resulted negative. His medical history started with an acute episode of sinusitis successfully treated with NSAIDs, and shortly after he went to the ER for an acute episode of epigastralgia, where he was discharged under omeprazole for a suspected gastritis.

About one week later he reported recovery of epigastralgia relapsed, irradiating to the right hypochondrium, associated to nausea. He went to the ER again: the physical examination showed signs of peritonism, while the bedside ultrasound evaluation revealed bilateral medium-basal pleural effusion, with bilateral pulmonary thickening, air bronchogram, circumferential pericardial effusion >1 cm, mild liquid flap in the Douglas and thickened gallbladder wall. The patient was then admitted in our Department of Internal Medicine.

At the presentation on ward the patient appeared alert and orientated, apyretic and eupneic, with normal vital signs. Laboratory tests showed normal white blood cells count with eosinophilia, raised levels of inflammatory markers, transaminases and cholestatic indexes (Table 1).

Chest x-ray performed on the first day of hospitalization showed obliterations of cost-frenic angles bilaterally in the absence of signs of focal parenchymal inflammation; thoracic-ultrasound confirmed bilateral pleural effusion. Abdominal ultrasound showed mild hepatomegaly with homogeneous structure, with no focal lesions, thickened gallbladder walls containing sludge and micro calculi, mild splenomegaly with patent and normal splenoportal axis, regular suprahepatic veins, and a moderate peritoneal effusion.

On day 3 the patient underwent both diagnostic and evacuative thoracentesis, with extraction of 1050 cc of pale yellow pleural liquid with features of exudate according to Light’s criteria (ph 7.436, LDH 228 U/L; LDH pleura/serum =0.97). Cytological examination revealed inflammatory pleural fluid rich in eosinophil granulocytes.
In order to rule out infectious or autoimmune hepatopathy, multiple serological tests were performed and they all turned out to be in the normal range. HIV, CMV, Parvovirus B19, HEV, HAV, HBV, HCV, Herpes Simplex Virus, Epstein Barr Virus, Toxoplasma, Leptospirosis, Micoplasma pneumoniae, Adenovirus, Enterovirus, Borrelia burgdorferi, Bordetella, Rickettsia, Echinococcus, Amoebiasis, Toxocara, Anisakis, Quantiferon, and stool sample for parasites were tested and proved negative for active infection. Immunology tests like lymphocyte typing, dosage of TSH, LDH, beta2microglobulina, ANA, ASMA, LKM, ENA, antiDNA, FR, MPO ANCA, PR3 ANCA, serum trypsin, Rast tests, resulted in the normal range.

We completed the investigations with a CT scan. The CT confirmed bilateral pleural effusion, in the absence of parenchymal nodular formations or mediastinic adenopathies, with minimal pericardial effusion. It also evidenced hypodense ilar hepatic tissue of 2 mm associated to perihepatic fluid and hilar, mesenteric and lomboaortic enlarged adenopathies. Therefore, because of the cholangitic pattern was most important, a MR cholangiography (Figure 1) that showed a stenosis of the right hepatic duct extended for 12 mm, likely due to the extrinsic compression of a kind of solid tissue, with no dilatation of the biliary ducts, and a distended gallbladder with minimal wall thickening, consistent with acute cholecystitis.

In order to rule out biliar tract tumors, a the PET scan (Figure 2) was performed. It showed high uptake of the radioactive tracer in the hepatic hilum and in the peripancreatic liquid (SUV 7.23).

An empiric treatment with ciprofloxacin plus ursodeoxycholic acid was started, with a partial improvement of the inflammatory markers, transaminases and cholestatic indexes. Considering the clinical improvements, we decided to delay the execution of any further investigations, such as percutaneous cholangiography (because of the high pancreatitis risk and at the same time the absence of a biliary tract dilatation) endobiliary brushing or liver
biopsy, after a one-month MRI re-evaluation. The patient was discharged with the diagnosis of polisierositis in a cholestatic hepatitis causing the inflammation of the main biliary duct.

The patient carried on examinations in the outpatient clinic. Laboratory tests showed a raise in eosinophilia and a progressive reduction of hepatic cytolysis indexes (Table 1). On the other side the patient presented a progressive increase in dyspnoea. Chest x-ray showed a gradual increase in pleural effusion especially in the right lung (Figure 3). Abdominal MRI was repeated one month after the previous one: at this time the right hepatic duct appeared patent while the left duct was inflamed and stenotic with an upward dilatation, and gallbladder showed minimal wall thickening. It also detected a lesion (25x11 mm) in the hepatic hilum at the emergence of the left hepatic duct, with tumor like appearance and possibly consistent with an inflammatory pseudotumor or a peripheral cholangiocarcinoma. Moreover there was abundant abdominal and pleural effusion and enlarged mesenteric lymphnodes.

After 8 days from the MRI abdominal ultrasound could not detect the hepatic hilar lesion anymore, but showed a persisting inflammatory aspect of the main biliary duct. Considering the raise in eosinophilia at the blood tests, the persistence of blood and radiological signs of inflammation, we repeated tests for parasites and bacteria, this time including the sierology for Strongyloides stercoralis, which turned out positive (anti-strongyloides IgG antibodies). Stool sample confirmed the presence of Strongyloides stercoralis larvae.

The patient underwent a five-days antibiotic course of Ivermectin per os. Nevertheless he was still experiencing dyspnoea for moderate efforts so that a chest X-ray was repeated and reported persistence of bilateral pleural effusion. Another evacuative thoracentesis was repeated and the patient gradually improved.

A further radiogram performed three months after the treatment showed a complete
resolution of the pleural effusion. At this time also serologies and stool examinations for Strongyloides resulted negative.

Since then the patient have been experiencing good clinical conditions.

We concluded that he probably ran into the aforementioned nematode because of his job in a waste disposal site and also because of the onychophagia he suffered for.

**Discussion and Conclusions**

It is estimated that about 100 million people worldwide have been infected by strongyloidiasis. Strongyloidiasis is endemic in rural areas of tropical and subtropical countries. In the past, the infection has also been reported in countries with temperate climate, like Italy.

Larvae live in moist soil and can infect humans the by skin contact. Unlike other helminthic parasites, Strongyloides can complete its life cycle entirely within the human body. The human cycle involves larvae that penetrate the skin, spread into the bloodstream and reach the right heart and then the lungs, where they penetrate into alveolar air sacs. The larvae then ascend bronchi, trachea and larynx and are swallowed. In the small intestine (duodenum and jejunum) they become adult worms, which produce eggs becoming rhabditiform larvae (smaller non-infectious larvae). The rhabditiform larvae mature into filariform larvae that can penetrate the perianal skin and give a start to an autoinfection, with the risk of disseminated disease especially in immunosuppressed patients (e.g. congenital and acquired immunodeficiency as HTLV-1 and HIV infections, underlying malignancy, malnutrition, alcoholism, hematopoietic stem cell transplantation, chronic use of steroids or cytotoxic drugs, etc). The massive dissemination of larvae to the lungs, liver and other organs may induce severe inflammation with symptomatic organ dysfunctions, like in our patient’s case, and even septic shock.
Finally if defecation takes place outdoors, the feces of the host can infect the soil and spread the infection.

Most of the infected patients have no prominent symptoms. If present, the most common gastrointestinal manifestations include abdominal pain, diarrhoea, and involuntary weight loss with malabsorption signs, nausea and vomiting. Pulmonary manifestations include dry cough, throat irritation, wheezing and hemoptysis. Some patients with chronic strongyloidiasis can present some kind of recurrent bacterial pneumonia or can develop asthma that characteristically worsens with corticosteroid use. There could be a cutaneous reaction where larvae penetrate the skin, urticarial areas near to the anus, but also migrating skin rashes (raised and transient pink lesions related to the dermal migration of larvae, the so-called running larvae), with pruritus.

The detection of rhabdiform larvae in stool samples or through serological tests usually makes the diagnosis of uncomplicated strongyloidiasis. However stool examination is often insensitive for detecting Strongyloides because larvae are excreted only intermittently and this might explain the delay in detecting larvae in the stool sample of our patient case. In disseminated strongyloidiasis, larvae can be found also in sputum, bronchoalveolar lavage fluid, and pleural, peritoneal and surgical drainage fluid. Polymerase chain reaction (PCR) tests have been shown to be more reliable for detecting Strongyloides compared with parasitological methods. Finally, larvae may be visualized by skin biopsy in patients with rash.

The appropriate treatment for strongyloidiasis is ivermectin with albendazole as an alternative.

Ivermectin is administered as two single 200 mcg/kg doses on two consecutive days, while albendazole 400 mg as twice daily for three to seven days. Literature reports lower efficacy for albendazole than ivermectin.
The prognosis of strongyloidiasis is usually good except in case of disseminated infection (hyperinfection syndrome), which could be lethal especially in people with weakened immune systems.\textsuperscript{15}

The blurred clinical presentation in an immunocompetent patient, living at unusual latitudes for this type of parasite, delayed our diagnosis and made it complicated. Moreover, we observed a transformative multi-organic involvement: from a predominantly abdominal pattern with epigastric pain, cholestatic hepatitis with migrating stenosis of the main biliary duct, to a change within few days into a prevailing pulmonary involvement, with increasing dyspnoea, polyserositis and eosinophilic pleural effusion.

Excluding other causes of eosinophilic pleural effusion (Table 2), keep in mind a helminthic parasites.

In conclusion, this wide range of clinical presentations, the non-specificity of laboratory parameters, makes the diagnosis of strongyloidiasis definitely challenging for the clinicians.

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Table 1. Baseline laboratory investigation.

| Parameter          | 1st value | 2nd value (1 month later) | Reference range |
|--------------------|-----------|---------------------------|-----------------|
| Hemoglobin (g/dL)  | 15.3      | 15.2                      | 13.5-17.0       |
| Red globe (× 1012/L) | 5.18     | 10.70                     | 4500-5700       |
| HCT (%)            | 44.7      | 44.1                      | 40.0-52.0       |
| MCV (fL)           | 86.3      | 83.9                      | 80.0-95.0       |
| MCHC (g/dL)        | 34.2      | 33.3                      | 32.0-36.0       |
| PLT (× 109/L)      | 388       | 398                       | 140-400         |
| White cell count (× 109/L) | 8.48 | 10.05                    | 4000-10000      |
| Neutrophils (%)    | 54.7      | 55.1                      | 40-70           |
| Lymphocytes (%)    | 23.1      | 27.2                      | 20-45           |
| Monocytes (%)      | 0.81      | 10.4                      | 3-10            |
| Basophils (%)      | 0.8       | 0.5                       | 0-1.5           |
| Eosinophils (%)    | 11.8      | 12.8                      | 0-6             |
| CRP (mg/L)         | 20.4      | 2.89                      | <5              |
| AST (U/L)          | 390       | 22                        | <41 male        |
| ALT (U/L)          | 595       | 25                        | <41 male        |
| Alkaline phosphatase U/L | 455 | 172                     | 40-129 male over 17 y |
| GGT U/L            | 557       | 124                       | 8-61 male       |
| Total bilirubin (mg/dl) | 1.08 |                       | <1.20           |
| Direct bilirubin (mg/dl) | 0.53 |                       | <0.30           |

Table 2. Some causes of eosinophilic pleural effusion and reasons of exclusion for our case.

| Causes of eosinophil pleural effusion | Reasons for exclusion of our case |
|---------------------------------------|-----------------------------------|
| Pneumothorax                          | Excluded with CT                  |
| Haemothorax                           | Excluded with thoracentesis       |
| Pulmonary infarction                   | Excluded with CT                  |
| Several thoracentesis                 | Perform 2 thoracentesis only      |
| Neoplasia                             | No evidence of solid or haematological neoplasms |
| Lymphoma                              | No evidence of lymphoma           |
| Disorder                  | Status                                      |
|---------------------------|---------------------------------------------|
| Tuberculosis              | Quantiferon negative                        |
| Pneumotoxicity (www.pneumotox.com) | The patient does not take any medication continuously |
| Asbestosis                | No evidence                                 |
| Parasitosis               | Strongiloides stercoralis positive on stool sample |
| Mycotic infection         | Negative laboratory serological investigations |
| Churg-Strauss Syndrome    | ANCA negative                               |

Figure 1. The subsequent MR cholangiography showed a stenosis of the right hepatic duct.
Figure 2. PET scan showed high uptake of the radioactive tracer in the hepatic hilum and in the peripancreatic liquid (SUV 7.23).
Figure 3. Chest x-ray showed a gradual increase in pleural effusion especially in the right lung.