Disseminated CMV and Tuberculosis Infection with Osseous Metaplasia in a Presumable Crohn’s Patient: Case Report

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ABSTRACT

Associations of different pathologies are not uncommon in everyday practice, but association of disseminated infections like cytomegalovirus infection and tuberculosis are quite rare and hard to diagnose. Both are infections which appear frequently in immunocompromised patients and have unfavorable prognosis. We present a case of a 62 year old male with a history of Crohn’s disease and tuberculosis which presented with symptoms of relapse and infection. He was treated with immunosuppressive medication and cortisol for the past 6 weeks. Cytomegalovirus (CMV) infection was serologically confirmed. In evolution, he suffered from gastrointestinal hemorrhage and died afterwards due to the hemorrhage and pulmonary infections. Histology confirmed the CMV modification in the lungs and intestines, but also highlighted active and disseminated tuberculosis (TB), bronchopneumonia, osseous metaplasia, hyaline membranes, numerous TB abscesses in the intestinal wall and specific CMV and TB modifications in the liver. The trigger for such important and serious infections remains unclear, for the cause can be represented by the Crohn’s disease per se or only by the immunosuppressive treatment. Also, CMV can trigger modifications in immune system and patients with immune-mediated diseases have an increased risk for TB reactivation.

Keywords: cytomegalovirus, tuberculosis, Crohn’s disease, osseous metaplasia, gastro-intestinal hemorrhage

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Article received on the 17th of February 2015. Article accepted on the 26th of June 2015.
INTRODUCTION

Various pathologies can lead to immunosuppression, including HIV infection, diabetes or, the most common, steroid treatment. In this instance, we present a case of a man with presumable Crohn's disease, treated with 5-ASA (azathioprine) and cortisol, which developed disseminated cytomegalovirus (CMV) infection and reactivation of tuberculosis. Also, bronchopneumonia, hyaline membranes, osseous metaplasia and intestinal fungal colonies were seen in histological slides.

Cytomegalovirus infection counts for almost 80-90% of the US population (1) and it is a frequent complication in immunocompromised patients and in patients with inflammatory bowel disease (IBD) due, not only to the treatment, but also to malnutrition or dysfunction of the immune system (2). In immunocompetent patients, clinical manifestations of CMV infection are rare (3) but IBD patients can present fever, cervical lymphadenopathy, splenomegaly, leucopenia, thrombocytopenia and pancolitis (2). Crohn's disease, as well as ulcerative colitis, is an inflammatory bowel disease, and appears histologically as a granulomatous, non-specific inflammation of the gut. Tuberculosis affects the lungs primarily, but, in immunocompromised patients with reactivation, multi-organ tuberculosis can be seen. Because of the increasing prevalence, HIV and TB are considered by the World Health Organization (WHO) as pandemic (4). More than 20% of the TB cases in US are extrapulmonary, manifesting especially as intestinal TB, with fever, abdominal pain, intestinal obstruction, fistulae or malnutrition, demanding a clear differential diagnosis with Crohn's disease, carcinoma or periappendicular abscesses (4).

Osseous metaplasia or bony metaplasia is a rare pathology, mostly identified postmortem (5-7). It appears in association with pulmonary fibrosis, chronic pulmonary disease (5) or interstitial lung disease (6). Other studies revealed an association of osseous metaplasia with tuberculosis (5).

CASE REPORT

We report a case of a 62 year old male, non-smoker, known with residual tuberculosis and Crohn's disease diagnosed five years ago in a different clinic and treated with 5-ASA and steroids for the past 6 weeks. He was admitted at the Bucharest Emergency University Hospital with weight loss, loss of appetite and diarrhea. From the patient's family history we highlight that his daughter had a spontaneous abortion due to a maternal infection with cytomegalovirus. Clinically, the patient was underweight, pale and presented with abdominal pain but without any palpable tumors. Paraclinical investigations showed inflammatory syndrome. The colonoscopy revealed a high number of ulcers with necrosis, mucus and blood as well as a caecum nodule with ulceration. The symptoms were considered to express a recurrence of the Crohn's inflammation. The patient developed pain during deglutition, productive cough and malnutrition symptoms under steroid and antibiotic treatment and an inferior gastrointestinal bleeding episode, which worsened respiratory symptoms. A suspicion of cytomegalovirus was raised and confirmed through serologic methods. Tuberculosis was clinically proved to be inactive. An antiviral treatment could not be initiated due to severe thrombocytopenia. The patient went into respiratory arrest after another inferior gastrointestinal bleeding and could not be resuscitated. The clinical diagnoses were bacterial and CMV pneumonia, Crohn's disease with CMV infection, severe thrombocytopenia and lymphopenia due to immunosuppression.

The autopsy revealed a patient with cachexy, numerous pigmented nevi, bilateral bronchopneumonia with edema, bilateral serous pleuresia, bronchectasia and numerous areas of anthracotic pigmentation. Multiple ulcerations and stenoses in the intestines with intestinal hemorrhage were observed, as well as a caecum exophytic mass with ulceration and necrosis that mimics a malignant tumor. Tissue samples were processed by conventional histopathological method using inclusion in paraffin and hematoxylineosin staining.

Histopathology from the lungs confirmed the bronchopneumonia, hyaline membranes and cytomegalovirus infection. Many granulomas were seen, consistent with active tuberculosis. Some areas presented nodules formed by lamellae of collagen with concentric distribution around various pigmented arias suggestive for silicotic nodule. Osseous metaplasia with marrow is observed on one slide (Figure 1). The liver presented cholestasis, congestion, caseous
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A Journal of Clinical Medicine, Volume 10 No.2 2015

granulomas (Figure 2) and lesions suggestive of CMV infection. The endothelial and epithelial cells from the colon also presented CMV inclusions associated with many abscesses and tuberculous lesions (Figure 3), confirmed by Ziehl Neelsen straining. The diagnostic criteria for Crohn’s disease could not be highlighted. The ulcer from the caecum contained necrosis, fibrin material with mixed inflammatory infiltrate and erythrocyte extravasation. Also, colonies of fungi were seen on HE and PAS staining was positive on the slides taken.

DISCUSSION

Classically, Crohn’s disease is an IBD affecting any part of the gastrointestinal tract, but occurring most commonly in the terminal ileum (8). It is a chronic inflammation from T-cell activation (9) leading to specific tissue injury. One of the many complications of IBD is CMV infection, appearing mostly in steroid-refractory forms of colitis, aggravating the course of the disease (10,11). CMV is affecting more than 40% of the global population (11), some studies claiming an incidence of 80-90% of the US population (1). The main method of CMV transmission in this case is unknown, and probably a transfusion in the past could explain the father-daughter co-infection. Although many studies sustained that CMV appears in refractory IBD and in association with immunosuppressive treatment (8), other studies fail to demonstrate the correlation between CMV and clinical severity of the IBD (12) as well as the correlation between the treatment for the infection and the reactivation of CMV (2). On the other hand, it is stipulated that CMV infection is a driver of profound immune changes (13).

Tuberculosis is believed to affect one third of the global population, mostly in developing countries (13). The low level of lymphocytes and the history of TB should have raised the suspicion of the reactivation. Even so, the tuberculin test can turn out negative due to the dysfunction of the immune system. TB is not infrequent in our country but disseminated tuberculosis is a rare diagnosis these days. Intestinal TB symptoms should be differentiated of those in Crohn’s disease or carcinoma and massive intestinal hemorrhage can appear due to tuberculosis, especially in association with CMV in HIV patients (4).

Our patient was diagnosed in another clinic with Crohn’s disease and treated with immunosuppressive medication, which lead to lymphopenia. Grossly, he presented with multiple ulcerations throughout the small and large intestine, complicated with different degree of stenoses but without any thickened wall. We did not manage to highlight the histological diagnosis criteria for IBD but the CMV and TB infection were, without any doubt, disseminated through the colon, lungs and liver. The exophytic mass found in the caecum also presented caseous necrosis with inflammatory infiltrate representative for ulcero-hypertrophic type of tuberculosis. These forms of tuberculosis are specific for gastric and duodenal TB and combinations of these lesions often occur (14).
The main differential diagnoses of ulcero-hypertrrophic tuberculosis must be done with inflammatory bowel disease and malignacies (15). We cannot tell for sure if the CMV infection was due to the pathogenicity of Crohn’s disease or to the immunosuppressive treatment, or that the gastrointestinal hemorrhage appeared as a symptom of IBD, of CMV or of the tuberculosis abscesses. Some studies revealed that patients with immune-mediated diseases have an increased risk of TB (16) raising the suspicion that tuberculosis had probably occurred due to the immunosuppressive treatment. Pathological features of intestinal TB lesions are difficult to distinguish from Crohn’s inflammatory lesions, leading to incorrect or delayed treatment (17). The PAS positive fungal colonies found throughout the intestines sustains the immunosuppression status. In what concerns the lung pathology, a mixture of bacterial bronchopneumonia, CMV infection and reactivated tuberculosis with silicotic-like nodules were histologically observed. A hypothetic explanation for such many granulomatous affections, some studies demonstrated an increased osteopontin gene expression identified by immunohistochemistry in TB and silicosis (18). Osseous metaplasia was also found in our case, leading to the presumption that there was an underlying chronic pulmonary pathology. Many studies highlighted the coexistence of bony metaplasia and tuberculosis (5) without any clinico-pathological implications.

**CONCLUSION**

The case presented above is a complex one, with a multitude of pathologies, mostly in association with the immunosuppressive treatment. The patient presented with a clear suppression explaining the majority of the pathologies. The interactions of these infections are, without any doubt, relevant factors for the unfavorable evolution of the patient and had an important role in the poor prognosis. Also, the presumable Crohn’s disease, can be a significant cause of the pathologies, but, the diagnosis remains questionable because we did not find any histological criteria. Furthermore, the treatment applied was, for sure, a relevant pawn for the immunosuppression of our patient and remains problematic in this context. The trigger for all those infection is unclear and remains a challenge both for pathologies and for clinicians.

**Conflict of interests:** none declared

**Financial support:** This work received financial support through the project entitled: “CERO – Career profile: Romanian Researcher”, grant number POSDRU/159/1.5/S/135760, cofinanced by the European Social Fund for Sectoral Operational Programme Human Resources Development 2007-2013.
with chronic multi-drug resistant tuberculosis: a case report. *J Med Case Rep* 2010;4:156


