

PROLONGED FEBRILE SYNDROME IN A PATIENT WITH INFLAMMATORY BOWEL DISEASE

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Abstract

Patients with inflammatory bowel disease (with or without immunosuppressive treatment) have a fragile immune status that predisposes to opportunistic infections. Cytomegalovirus (CMV) is an opportunistic pathogen that determines a large variety of clinical syndromes especially in immunocompromised patients. In inflammatory bowel disease (IBD) patients, his role has long been debated and it is thought that it can complicate the course of the disease. The most frequent clinical manifestation in inflammatory bowel disease patients is represented by CMV colitis, however other clinical manifestations can be met and must also be considered.

We present the case of a young male patient with ulcerative colitis that came to our attention for prolonged febrile syndrome and IBD flare, that was finally confirmed to have CMV disease.

Keywords: cytomegalovirus, CMV colitis, CMV mononucleosis syndrome, pseudotumor, CMV disease

Rezumat

Pacienții cu boli inflamatorii intestinale (cu sau fără tratament imunosupresor) au un status imun fragil, ce predispune la infecții oportuniste. Citomegalovirusul (CMV) este un patogen oportunist care determină o mare varietate de sindroame clinice, în special la pacienții imunocompromiși. La pacienții cu boli inflamatorii intestinale, rolul său a fost îndelung dezbătut și se crede că poate complica evoluția bolii. Cea mai frecventă manifestare clinică la pacienții cu boli inflamatorii intestinale este colita CMV; totuși și alte manifestări clinice pot fi întâlnite și trebuie luate în considerare.

Am prezentat cazul unui bărbat tânăr cu colită ulcerativă ce a ajuns în atenția noastră pentru sindrom febril prelungit și puseu al bolii inflamatorii intestinale și care în final a fost confirmat a avea boală CMV.

Cuvinte cheie: citomegalovirus, colita CMV, sindrom mononucleozic CMV, pseudotumoră.



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Abbreviations

CMV - cytomegalovirus, DNA - deoxyribonucleic acid, PCR - polymerase chain reaction, H&E - hematoxylin eosin, IHC - immunochemistry, IBD - inflammatory bowel diseases, HIV - human immunodeficiency virus, ECCO - European Crohn's and Colitis Organisation

Case presentation

A 43-year-old male patient presented at the emergency room for fever, chills and headache that worsened during night, debuted for 2 weeks. Three days before the presentation, bloody diarrhea added to the other mentioned complains.

Personal history of the patient showed a diagnosis of ulcerative proctitis, that was made 15 years ago, for which he was undergoing treatment with Mesalamine suppositories 1 g/day. However, he admitted that he has not been taking the treatment for the last 4-5 months and that the last endoscopic check-up was 2 years ago, when the lower gastrointestinal endoscopy showed a good control of the disease.

Clinical examination showed hypogastric pain with palpation, absence of adenopathy and bilateral purpura at the level of the calves (Figure 1, Figure 2). No splenomegaly or hepatomegaly were detected.

Laboratory tests revealed leukocytosis with high levels of lymphocytes and monocytes

(leucocytes - 14,99 k/ μ L, monocytes - 1,15 k/ μ L, lymphocytes - 9,7 k/ μ L), mild liver cytolysis (GPT - 280 U/L, GOT - 124 U/L), cholestasis (GGT - 142 U/L, PAL - 140 U/L) and an inflammatory syndrome (CRP - 76,98 mg/L). The patient denied drinking alcohol and smoking. Considering the clinical and biological picture of the patient, it was decided to initiate an empirical broad-spectrum antimicrobial treatment.



Figure 1. Bilateral purpura at the level of the calves



Figure 2. Bilateral purpura at the level of the calves



Figure 3, Figure 4. Pseudotumor lesion of the duodenum 2 revealed by upper digestive endoscopy



Figure 5, Figure 6, Figure 7, Figure 8, Figure 9. Numerous ulcers of the colon revealed by lower gastrointestinal endoscopy



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Prior to initiating antibiotic treatment, an infectious screening was made, and it showed negative hemocultures, negative urine cultures, negative stool cultures and absence of ova and parasites in the stool, negative RT-PCR SARS-COV2. Serology for HIV, hepatitis B, hepatitis C, hepatitis A, Herpes simplex virus, Epstein-Barr virus and varicella zoster virus were all negative. Quantiferon test and sputum cultures were also negative.

Serology for cytomegalovirus was also performed and showed positive IgM and IgG for CMV. Given the prolonged febrile syndrome, heart ultrasound was performed, which excluded an infectious endocarditis. Although the neurological exam did not reveal any acute neurological deficit, a cerebral CT exam was performed to exclude an organic lesion.

After 5 days of antibiotic treatment, the clinical status of the patient improved with a decrease of the number of stools, amelioration of the stool consistency, remission of the bloody diarrhea, but with the persistency of the headache.

Given the improvement of the digestive symptoms, it was decided to perform an endoscopic check-up. The upper digestive endoscopy revealed a lesion of the duodenum 2 and biopsies were taken (Figure 3 and Figure 4). Lower gastrointestinal endoscopy showed increased friability of the mucosa that bled

when touched by the scope, with numerous ulcers that stretched from the rectum to the left colic flexure.

The lesions spared the transvers and the ascending colon but were met again in the caecum. The ileum was normal. Several biopsies were taken, both for histopathological exam and for CMV diagnosis (Figure 5, Figure 6, Figure 7, Figure 8, Figure 9).

Investigations were completed by quantitative assay of CMV by PCR that showed 15016 /ml copies. Ophthalmology consultation was asked to exclude retinitis. Neurology reevaluation was also demanded, but neurologist opinion was that there were not enough reasons to justify an CMV encephalitis as cause of the headache.

Treatment by Valganciclovir 450 mg x 4/day was started and continued for 30 days. Meanwhile patient was continued on Mesalamine both oral and suppositories. Five days after the antiviral treatment was started, there was a major improvement of his general wellbeing with complete remission of headache, fever, and normalization of the stools.

Discussion

Cytomegalovirus is an enveloped double-stranded DNA virus from the Herpesviridae family. Humans represent the only natural host, and the transmission is made through

close contact with body fluids like saliva, blood, urine, genital secretions, breast milk. It infects several cell types, integrates in human DNA, and persists lifelong in his latency form⁽¹⁾.

Cytomegalovirus can cause symptoms through primary infection or through reactivation. CMV infection doesn't equal CMV disease and difference between these two entities must be made. CMV infection means there is evidence of CMV replication, while CMV disease signify that the patient presents both evidence of infection and symptoms caused by infection⁽²⁾.

It can cause a wide range of clinical manifestations that may vary from CMV colitis to retinitis, pneumonitis, encephalitis, purpura, hepatitis, and prolonged febrile syndrome. However, these manifestations are rarely met in immunocompetent patients⁽⁶⁻⁷⁾.

The most frequent clinical manifestation of CMV infection in immunocompetent patients is CMV mononucleosis syndrome. This syndrome is characterized by sore throat, prolonged febrile illness, atypical lymphocytosis, and anicteric hepatitis. Cervical adenopathy and hepatosplenomegaly are more common in Epstein-Barr mononucleosis syndrome comparative with CMV mononucleosis syndrome, and these characteristics can help to differentiate between them^(6,8,9).

In immunocompromised hosts CMV infections determine more severe disease. Among the immunocompromised categories that are more prone to develop symptoms from CMV infections are solid organ grafts recipients, HIV patients, patients undergoing chemotherapy or immunotherapy, pregnant women and patient receiving hematopoietic stem cells transplantation⁽¹⁰⁾.

In IBD patients the reactivation is stimulated by the inflammation in severe forms of the disease but also by the therapies prescribed.

Glucocorticoids and immunosuppressive therapies like azathioprine, methotrexate, cyclosporin seem to increase the risk of viral reactivation while anti-TNF and 5-aminosalicylates are not associated with such risk. The most frequently met clinical manifestation in IBD patients is CMV colitis, but the other syndromes can be met too⁽¹¹⁾.

In the case we presented, the patient had a complex clinical picture which included mononucleosis syndrome characterized by lymphocytosis and prolonged febrile syndrome, anicteric hepatitis, purpura, and colitis. In the beginning, the presence of the prolonged febrile syndrome among with the headache determined us to perform an extensive infectious screening, but in the end, we concluded that these symptoms were part of the clinical panel of cytomegalovirus disease.

There are several diagnostic tests that can be performed to detect CMV infection. These include blood tests like serology (IgM and IgG), PCR CMV DNA test from blood, pp65 antigen and histology tests like PCR CMV DNA test from tissue, H&E staining and IHC^(12,13).

In our case, the choice between different diagnostic tests was influenced by their availability in our center. Serological tests and PCR CMV DNA helped us made a positive diagnosis of CMV disease, but the biopsies from colon were negative for CMV inclusions. Unfortunately, the possibility of performing IHC and PCR CMV DNA was not available in our center. Serology tests consist of CMV IgG and IgM determination. While IgG are representative of past infection, IgM antibodies are indicators of acute or recent infection, but it has to be said that determination of IgM titers has its limitations⁽¹⁴⁾. CMV IgM titers rise 2-3 weeks after the acute primary infection and continue to drop slowly 2-3 months afterwards. CMV serology should be interpreted together



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with a second test, when making a diagnosis of CMV infection^(15,16).

PCR CMV DNA from blood makes a quantitative determination of the level of viral replication in the blood. Studies on patients that received a solid organ transplantation showed that a high viral load in the plasma correlates with a more severe disease⁽¹⁷⁾.

ECCO guidelines recommend immuno-histochemistry and tissue polymerase chain reaction for confirming CMV colitis in IBD patients⁽¹⁸⁾. The biopsies that we took didn't show any CMV inclusions on H&E staining, but we didn't get to perform neither tissue PCR, nor immunochemistry because they weren't available in our center. So given the suggestive clinical signs and the high viral load a diagnosis of CMV disease was made, but a definitive diagnosis of CMV colitis could not be confirmed. However, later on, clinical improvement of gastrointestinal signs was seen on antiviral treatment.

There is a constant debate in the literature regarding the role of the CMV in the pathogenesis and the progression of the inflammatory bowel disease, and while there is still a long way to end this debate what we already know is that a fair distinction between a flare of ulcerative colitis and CMV colitis can be difficult to make⁽¹⁹⁾.

The patient we presented was already known with ulcerative proctitis and whether that CMV caused a flare of the IBD or the lack of

compliance to treatment favored the flare remains questionable. In our opinion a mixed mechanism involving both was the cause.

Endoscopy might be necessary to take biopsies and to evaluate the extension of the lesions. There are several studies that tried to identify endoscopic lesions suggestive of CMV colitis and they showed that punched-out ulcers, geographical ulcers, and deep ulcers are more frequently met in CMV-positive ulcerative colitis patients, than in those that do not have the infection. However, a definitive diagnosis of CMV colitis cannot be supported just by endoscopic findings and complementary tests are necessary for diagnosis^(20,21).

In our patient colonoscopy showed punched-out ulcers and irregular ulcers as well as granularity and friability of the rest of the affected mucosa. An endoscopic particularity we found in this case was the presence of a pseudotumor in the duodenum

2. The biopsies from this lesion were positive for lymphoplasmacytic infiltrate in lamina propria, modification suggestive of duodenitis. Pseudotumor lesions secondary to CMV infection were described before in the literature, especially in HIV patients. These type of lesions were described in the colon, rectum, stomach or duodenum and a decrease in size was observed after antiviral treatment⁽²²⁻²⁶⁾.

ECCO guidelines recommend treating CMV colitis with intravenous ganciclovir for 5-10

days, than switching to valganciclovir for another 2 weeks⁽⁸⁾.

In our case there was no definite diagnosis of CMV colitis, however given the persistent symptomatology and the high viral load, the decision to start antiviral treatment was made. Several reports showed that even the immunocompetent patients that present with persistent symptoms and active viral replication benefit from antiviral treatment, with faster remission of symptoms⁽²⁷⁾. Different studies have defined different plasma DNA cut-offs for various indications concerning the best moment to start the antiviral treatment, so there is still a lack of consensus⁽²⁸⁾. Oral Valganciclovir 900 mg daily was given for 3 weeks to our patient, while continuing treatment with Mesalamine both oral and suppositories. After five days of antiviral treatment, all the complaints were in remission. The net improvement of his general condition under the antiviral treatment supported once again the diagnosis of CMV disease.

The patient returned for clinical control at the end of the antiviral treatment when the remission of all the symptoms and the normalization of the biological panel could be observed. He continued treatment for ulcerative proctitis with mesalamine both suppositories and oral tablets.

Conclusion

Cytomegalovirus infection should always be searched when faced with a flare of ulcerative colitis. Even if CMV colitis is the most frequent manifestation of CMV infection in ulcerative colitis patients, sometimes the clinical picture can be more complex.

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