Cytomegalovirus immune reconstitution inflammatory syndrome manifesting as acute appendicitis in an HIV-infected patient

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Abstract:

We report the first case of CMV appendicitis as a manifestation of Immune Reconstitution Inflammatory Syndrome (IRIS). CMV appendicitis presents with typical appendicitis symptoms including surgical abdomen, fever and leukocytosis and may have a more severe course with higher mortality than other types of infective appendicitis.
Clinical case

Combination anti-retroviral therapy (ART) has reduced the mortality from cytomegalovirus (CMV) opportunistic infections in HIV positive patients [1]. CMV continues to result in morbidity and mortality in patients initiating ART at low CD4 T-cell counts, occasionally as a result of immune reconstitution inflammatory syndrome (IRIS). We present a case of unmasking CMV-IRIS in an HIV-infected patient following ART initiation.

The patient enrolled in an Institutional Review Board-approved, prospective study of HIV-1 infected, ART naïve patients with CD4 cell count below 100 T cells/µL in Bethesda, Maryland, one month after a new HIV diagnosis. At the time of enrollment, the patient complained of a 23 Kg weight loss and had a CD4 count of 72 T cells/µL and a plasma HIV-RNA of 284,010 copies/ml. The viral genotype showed wild type virus and she was initiated on Efavirenz/Emtricitabine/Tenofovir. Her blood CMV PCR was negative at baseline, CMV IgG was positive (4.460 U) and CMV IgM was negative.

Two weeks after ART initiation, the patient returned to care with a four-day history of cramping abdominal pain predominantly in the right lower quadrant as well as nausea and anorexia without chills, vomiting, diarrhea, urinary symptoms, or vaginal discharge. The patient was febrile (38.8°C) and tachycardic (124bpm). Abdominal exam revealed normoactive bowel sounds with direct tenderness to palpation in the lower abdominal quadrants (right more than left). Guarding, rigidity, and rebound were absent and the remainder of the exam was noncontributory.
CBC demonstrated leukopenia (leukocytes 2.58 K/µL) with 0.8% immature granulocytes. Alkaline phosphatase was 186 IU/L (up from 140 IU/L at baseline), with normal liver and pancreatic enzyme levels. The CRP had increased from 1.95 mg/dl at baseline to 8.52 mg/dl. Blood CMV PCR became detectable at 750 copies/ml. An abdominal CT scan demonstrated thickening of the appendix with fat stranding and mild lymphadenopathy of the pelvic sidewall, predominantly on the right side consistent with appendicitis. The patient underwent an uncomplicated laparoscopic appendectomy, received IV metronidazole and vancomycin perioperatively and was discharged on post-op day three.

Pathologic examination of the patient’s appendiceal tissue demonstrated appendicitis with sealed perforation and evidence of CMV infection. There was marked lymphoid hyperplasia with mature lymphocytes and plasma cells (figure 1A). Immunohistochemistry showed that the lymphocytic infiltration was composed of a mixture of T cells and polyclonal B cells with equal distribution of immunoglobulin light chain kappa and lambda staining, making lymphoma unlikely. Neutrophilic infiltration was rarely noted. In situ hybridization for EBV virus encoded small RNA (EBER) was negative. CMV viral staining was positive in numerous cells showing typical cytopathic changes of CMV infection, including cellular and nuclear enlargement and nuclear inclusions (figure 1B), and were distributed throughout the full thickness of the bowel wall.
The patient returned to clinic after 3 weeks with complaints of increased abdominal pain and two episodes of hematochezia. Valganciclovir was initiated for suspected CMV colitis (endoscopy could not be performed due to the abdominal surgery). The patient completed two weeks of valganciclovir therapy and was clinically improved.

**Review of the literature**

Appendicitis has been documented to occur with increased frequency in HIV infected patients as compared to HIV uninfected patients [3]. A number of opportunistic pathogens or AIDS related malignancies have been shown to cause appendicitis in HIV positive patients, including Kaposi sarcoma [3], Strongyloides [4], Mycobacterium tuberculosis [5], and Mycobacterium avium complex [6].

Tucker et al. published the first report of CMV appendicitis in an HIV positive patient in 1989 [7]. Since that time, ten additional reports of CMV appendicitis in HIV patients have been described in the literature [8-16]. Ten of the eleven reported patients presented with right lower quadrant pain and in eight of them fever was noted at the time of presentation (see Table 1) [7-16]. CMV appendicitis typically presents with similar symptoms [17,18], but may have a higher mortality than other identified etiologies of appendicitis [12, 17].

In a study of autopsies of HIV positive patients, CMV was the most commonly isolated opportunistic infection, though the vast majority of the patients were asymptomatic while alive [19]. In this particular patient, the biopsy demonstrated substantial inflammation
and necrosis as well as abundant CMV positive cells, making CMV the likely cause of appendicitis, rather than an incidental finding.

It has been hypothesized that appendicitis in HIV positive patients could be a result of IRIS, likely due to reactive lymphoid tissue in the appendix [20,21]. Although CMV-IRIS in HIV-infected patients has been mostly reported as uveitis in those with CMV retinitis [22], appendicitis can be a rare manifestation of CMV in this clinical setting.
Authors’ contributions
Virginia Sheikh and Sarah Kattakuzhy provided clinical care for the patient. Hao-Wei Wang provided the pathological diagnosis and images. Kimberly Faldetta, Virginia Sheikh, and Irini Sereti wrote the article.

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References


Table 1: CMV appendicitis cases reported in HIV-infected patients from 1988 to present.

<table>
<thead>
<tr>
<th>Reference/ Year</th>
<th>Age /Gender</th>
<th>ARVs at diagnosis (duration)</th>
<th>Clinical syndrome</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[6] 1989</td>
<td>35yo M</td>
<td>No</td>
<td>Abdominal pain, TTP in RLQ, rebound</td>
<td>Histology</td>
<td>Laparoscopic appendectomy with IV and oral antibiotics</td>
<td>Abscess; Recovery then readmission and death 25 days later</td>
</tr>
<tr>
<td>[7] 1988 (Published in 1991)</td>
<td>50yo M</td>
<td>No</td>
<td>Fever, RLQ pain, rebound tenderness, RLQ mass</td>
<td>Histology</td>
<td>Exploratory laparotomy; IV antibiotics ganciclovir 5x/week (“maintenance therapy”) when CMV confirmed</td>
<td>Periappendiceal abscess; Recovery</td>
</tr>
<tr>
<td>[8] 1990</td>
<td>28yo M</td>
<td>Yes (5 weeks)</td>
<td>RLQ pain, rebound</td>
<td>Histology</td>
<td>Exploratory laparotomy, IV antibiotics with appendectomy</td>
<td>Recovery</td>
</tr>
<tr>
<td>[10] 1993</td>
<td>38yo M</td>
<td>NR</td>
<td>RLQ pain, fever TTP at McBurney’s point</td>
<td>Histology, IHC (monoclonal anti-CMV antibody)</td>
<td>IV antibiotics and observation; Exploratory laparotomy with appendectomy; Ganciclovir</td>
<td>Recovery</td>
</tr>
<tr>
<td>Year</td>
<td>Age</td>
<td>Gender</td>
<td>History</td>
<td>Symptoms</td>
<td>Procedures</td>
<td>Outcome</td>
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<tr>
<td>1995</td>
<td>34yo M</td>
<td>Yes (unknown duration)</td>
<td>RLQ pain, fever</td>
<td>Histology CMV PCR in WBC</td>
<td>Laparoscopic appendectomy</td>
<td>Recovery</td>
</tr>
<tr>
<td>1997</td>
<td>30yo M</td>
<td>NR</td>
<td>RLQ pain, fever, nausea, vomiting</td>
<td>Histology</td>
<td>Appendectomy, post-op ganciclovir</td>
<td>Recovery</td>
</tr>
<tr>
<td>1997</td>
<td>29yo M</td>
<td>NR</td>
<td>Right sided abdominal pain</td>
<td>Histology, immunofluorescence</td>
<td>Appendectomy</td>
<td>Abscess and perforation; Recovery</td>
</tr>
<tr>
<td>2004</td>
<td>37yo M</td>
<td>NR</td>
<td>Fever, abdominal pain, rebound and guarding over RLQ</td>
<td>Histology, immunostaining</td>
<td>Appendectomy; IV ganciclovir</td>
<td>Recovery</td>
</tr>
<tr>
<td>Present case</td>
<td>38yo F</td>
<td>Yes (2 weeks)</td>
<td>RLQ pain, anorexia, nausea, fever</td>
<td>Histology, CMV viral staining</td>
<td>Laparoscopic appendectomy, IV antibiotics peri-operatively, valganciclovir (2 weeks)</td>
<td>Perforation seen; Full recovery</td>
</tr>
</tbody>
</table>

NR: not reported; M: male; F: female; RLQ: right lower quadrant; TTP: tenderness to palpation, IHC: immunohistochemistry. WBC: white blood cells.
Figure Legend

1A: Histopathologic examination by H&E stain showing lymphoplasmacytic hyperplasia and scattered enlarged cells (arrow) with features characteristic of CMV-induced cytopathic changes.

1B: CMV immunostaining demonstrating CMV-infected cells throughout the full thickness of the bowel wall (arrows). Figure inset illustrates an infected cell at higher power view showing cellular and nuclear enlargement with nuclear inclusions.