Corticosteroid-induced Kaposi’s Sarcoma Revealed by Severe Anemia: A Case Report and Literature Review

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Abstract:
We herein report a case of gastrointestinal (GI) Kaposi’s sarcoma (KS) without cutaneous involvement in a 73-year-old man who had received immunosuppressive drugs for granulomatosis with polyangiitis. After one year of prednisolone use, he presented with tarry stool and severe anemia. Endoscopic and pathological examinations revealed bright-reddish protruding lesions with proliferating spindle cells positive for D2-40, CD34, and HHV-8, which are definitively diagnostic of GI-KS. Drug-induced KS without HIV infection or transplantation is extremely rare, and its clinical features remain unknown. Therefore, we conducted a literature review of steroid-induced KS.

Key words: Kaposi’s sarcoma, granulomatosis with polyangiitis, steroid, immunosuppression

Introduction
Kaposi’s sarcoma (KS) is an angioproliferative disorder, the onset of which requires infection with human herpes virus 8 (HHV-8) (1). There are four presentations in which KS occurs: 1) the classic form, which typically presents in elderly persons of Mediterranean or Eastern European descent; 2) the endemic form, which has been described in indigenous peoples of Sub-Saharan Africa; 3) the iatrogenic form, which is associated with immunosuppressive drug therapy; and 4) the AIDS-associated form (2). The most common presentation is the AIDS-associated form (3), and iatrogenic KS is relatively rare. Steroids are the most widely used form of immunosuppressive therapy, but the typical background, management, and prognosis of patients with steroid-induced KS remain unknown. Furthermore, the management of steroid-induced KS may differ from that of other types of KS.

We herein report a case of gastrointestinal (GI)-KS who had received long-term steroid therapy for granulomatosis with polyangiitis. We also conducted a literature review of steroid-induced KS.

Case Report
The patient, a 73-year-old Mongolian man, had been diagnosed with granulomatosis with polyangiitis 1 year earlier. His treatment regimen consisted of high-dose cyclophosphamide 1,000 mg/month and systemic corticosteroids, intravenous methylprednisolone pulse followed by oral prednisolone 50 mg/day (Fig. 1). Remission was achieved, and cyclophosphamide was changed to azathioprine 50 mg/day, with prednisolone slowly tapered to 12 mg/day over 11 months (Fig. 1).

After 11 months of therapy, he was hospitalized for tarry stool. He had taken lansoprazole daily for 11 months and was not taking any nonsteroidal anti-inflammatory drugs (NSAIDs). On his initial presentation, his vital signs were stable, and gastrointestinal, cardiovascular, pulmonary, skin, and extremities examinations were normal. An HIV-RNA test, cytoplasmic-antineutrophil cytoplasmic antibody, and Helicobacter pylori antibody were negative. His hemoglobin concentration was 6.0 g/dL, so he received 6 units of red blood cell transfusion. The hemoglobin concentration then increased to 7.9 g/dL the next day and showed gradual improvement (Fig. 1).
Upper and lower GI endoscopy showed multiple bright-reddish protruding lesions with ulcers (Fig. 2). We found a total of 10 lesions in the stomach and 16 in the colon. No active bleeding was observed from any of the lesions. A biopsy of the lesions revealed the presence of proliferating spindle cells with vascular channels filled with blood cells on Hematoxylin and Eosin (H&E) staining (Fig. 3A). Immunohistochemical staining revealed the expression of the lymphatic vessel endothelial cell marker D2-40 (Fig. 3B) and the blood vessel endothelial cell marker CD34 (Fig. 3C). Some endothelial cells were also positive for HHV-8 LANA-1 (Fig. 3D).

A diagnosis of GI-KS was made based on the endoscopic and pathological findings. We considered that the development of GI-KS was associated with immunosuppression induced by steroid use and initiated treatment by withdrawal of prednisolone. Over the next 4 months, prednisolone was tapered to 6 mg/day. At five months after the diagnosis of GI-KS, repeat upper GI endoscopy showed that the ulcers and reddish lesions had become smaller, and marked improvement was noted after 13 months (Fig. 4). No clinical recurrence occurred during two years of follow-up.

Discussion

We identified several important clinical features in the present case. First, GI-KS can occur in isolation. KS manifests primarily as a cutaneous disorder, with visceral involvement (4). Nagata et al. reported that 75.8% of AIDS-associated GI-KS patient had cutaneous KS (5). Iatrogenic GI-KS without cutaneous lesions is considered rare. Second, GI-KS lesions were found in the esophagus, colon, and rectum, which was consistent with findings from a previous study (5, 6). Nagata et al. reported that GI-KS involvement was frequently found in the stomach, duodenum, colon, esophagus, and rectum, in order of increasing frequency (5), whereas Viazis et al. reported that GI-KS involvement was rarely found in the small intestine (6). We did not perform small intestinal endoscopy due to the invasiveness of the procedure and because an examination of the small intestine would not have altered the management or treatment in this case. Third, previous studies have shown distinctive endoscopic findings of GI-KS, such as reddish patches, a polyloid appearance, submucosal tumor-like lesions, and ulcerative submucosal tumor (7), which were detected in our case and facilitated the diagnosis. Fourth, a biopsy of the stomach revealed the presence of proliferating spindle cells with vascular channels filled with red blood cells on H&E staining (Fig. 3A), which is pathologically characteristic of KS (8). This is seen as reddish mucosa on endoscopy (Fig. 2). We believe that the abundance of red blood cells indicated a small amount of continuous bleeding, which in turn led to the severe anemia. Fifth, GI-KS was induced by steroid use, which is a particularly important feature of this
Figure 2. Endoscopic findings of upper and lower GI tract. A: Multiple reddish, flat lesions in the upper body of the stomach. B: Submucosal tumor-like lesion in the lower body of the stomach. C: Submucosal tumor-like lesion with ulceration in the antrum of the stomach. D: Reddish polypoid lesion in the descending colon. E: Submucosal tumor-like lesion with central ulcer in the sigmoid colon. F: Reddish submucosal tumor-like lesion in the ascending colon.

Figure 3. Histological findings of the biopsy specimen from the stomach. A: Low-power view showing a distinct proliferative lesion on Hematoxylin and Eosin staining and high-power view showing spindle cell proliferation with vascular channel formations filled with blood cells (×100, ×200). C: The vascular gaps are lined with endothelial cells when stained with D2-40 (×100). D: The vascular gaps are lined with endothelial cells when stained with CD34 (×100). E: Some endothelial cells are positive for HHV-8 (×100).
The characteristics, management, and prognosis of patients with steroid-induced KS remain unknown; thus, we reviewed the English-language literature in the MEDLINE database by searching with keywords “Kaposi’s sarcoma”, “steroid”, and “immunosuppression”. We excluded HIV-positive patients and post-transplantation patients and eventually identified 33 cases of iatrogenic KS due to systemic corticosteroid use (22 men, 11 women; mean age 56 years old, range 7-84 years old) (Table) (9-41). The underlying diseases included autoimmune disorders such as pemphigus vulgaris, bullous pemphigoid, rheumatoid arthritis, Behçet’s disease, ulcerative colitis, and Crohn’s disease. KS most frequently developed on the skin in 26 cases, followed by the GI tract in 11 cases. Of the 11 GI cases, isolated GI-KS accounted for 6 cases, all of which had ulcerative colitis or Crohn’s disease. The most commonly used steroid was prednisolone, and the amount of steroid used ranged from 2.5 to 80 mg/day. In 20 of 33 cases, discontinuation or tapering of the steroid dose was selected for treatment. Of these 20 cases, 14 (70%) showed improvement, while 6 (30%) did not. In our case, isolated GI-KS was induced by prednisolone that was being administered for the treatment of granulomatosis with polyangiitis. This is the first case of isolated GI-KS without inflammatory bowel disease. GI-KS was improved by tapering prednisolone to 6 mg/day.

In conclusion, KS can be seen in long-term steroid users even in the absence of HIV infection or transplantation. Steroids are the most widely used form of immunosuppressive therapy, and caution should be practiced in order to prevent the development of KS as an opportunistic infection. When patients on long-term steroid therapy present with overt GI bleeding and anemia, endoscopy with a biopsy seems to be essential for a definitive diagnosis.

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<table>
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<th>Reference</th>
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<th>Underlying disease</th>
<th>Lesion</th>
<th>Immunosuppressive drug</th>
<th>Treatment</th>
<th>Outcome</th>
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<td>UC</td>
<td>Colon</td>
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<td>Improvement</td>
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<td>MM</td>
<td>Skin</td>
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<td>Tapering of DEX Discontinuation of BOR and CPA</td>
<td>Initiation of lenalidomide</td>
<td>Improvement</td>
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<td>GPA</td>
<td>Skin</td>
<td>PSL (25 mg/d) AZA (150 mg/d)</td>
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<td>Therapy</td>
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<td>Therapy</td>
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<td>UC</td>
<td>Skin</td>
<td>Steroid (high dose)</td>
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<td>Improvement</td>
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<td>(39)</td>
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**Note:**
- **PSL:** Prednisolone
- **Aza:** Azathioprine
- **BOR:** Bortezomib
- **BP:** B cell lymphoma
- **MTX:** Methotrexate
- ** CYA:** Cyclosporine
- **Dex:** Dexemethasone
- **DLBCL:** Diffuse large B cell lymphoma
- **GVHD:** Graft versus host disease
- **SL:** Sulfasalazine

**Summary of 33 Cases of Steroid-induced Kaposi’s Sarcoma.**

- The study includes 33 cases of Kaposi’s sarcoma treated with various immunosuppressive drugs and their outcomes.
- The treatments varied from surgery to discontinuation of drugs, with some cases demonstrating improvement or no improvement.
- The outcomes included treatments such as surgery, discontinuation of drugs, and improvement.

**ATP:** Autoimmune thrombocytopenic purpura, **AZA:** Azathioprine, **BOR:** Bortezomib, **BP:** B cell lymphoma, **CD:** Crohn’s disease, **CPA:** Cyclophosphamide, **CYA:** Cyclosporin, **DEX:** Dexamethasone, **DLBCL:** Diffuse large B cell lymphoma, **GA:** Granulomatosis with polyangiitis, **IVG:** Intravenous immunoglobulin, **ITP:** Idiopathic thrombocytopenic purpura, **MM:** Multiple myeloma, **MTX:** Methotrexate, **PSL:** Prednisolone, **PTX:** Paclitaxel, **PV:** Pemphigus vulgaris, **RA:** Rheumatoid arthritis, **UC:** Ulcerative colitis.
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