Smoldering Multiple Myeloma Arising in Ulcerative Colitis

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To the Editor: A 67-year-old man presented with recurrent diarrhea and abdominal pain of increasing severity for 7 months in May 2016. He had mucopurulent stool for about 4–6 times a day, with bellyache, tenesmus, and weight loss. He took a colonoscopy, which showed universal colitis, and a biopsy revealed crypt abscesses and inflammatory cell infiltration and he was diagnosed with ulcerative colitis (UC). 5-Aminosalicylic acid (mesalazine) was administered, with symptoms remitted after 3 months. Not long, he presented with diarrhea again. He passed 7–8 liquid motions daily, containing blood and mucus, with fever and weakness. After admission, a repeated colonoscopy revealed continuous edema and erosions across the hyperemic colorectal mucosa, and a biopsy showed crypt abscesses and inflammatory cell infiltrations [Figure 1a and 1b]. Laboratory studies revealed hemoglobin of 107 g/L, and the white blood cell was 8.73 × 10^9/L, with 77.6% neutrophils. The total serum protein was 70 g/L and the globulin was 38 g/L. The serum folate, serum vitamin B12, serum iron, and total iron-binding capacity were normal. The erythrocyte sedimentation rate ranged from 31 to 45 mm/h (reference value, 0–15 mm/h), and the C-reactive protein was 92.5 mg/L (reference value <8.0 mg/L). His serum immunoglobulin G (IgG) level increased to 24.90 g/L (reference value, 7.51–15.60 g/L). M-protein (IgG-λ type) was found by routine examination of serum protein electrophoresis, which revealed an increase in γ globulin, accounting for 28.6% (reference value, 9.2–18.2%). Considering the possibility of plasma diseases, bone marrow aspiration was performed. The percentage of plasma cells in bone marrow was 8.5% accompanied by abnormal plasma cells with large binuclei, and a biopsy showed plasma cells scattered in the bone marrow [Figure 1c and 1d]. Red blood cell rouleaux could be seen. Flow cytometry findings were also compatible with plasma cell disease. After a comprehensive assessment, the patient was considered with recurrent UC and was recommended glucocorticoid therapy, but he refused. He was treated with mesalazine enema and bloody stool was under remission. Then, he was discharged from the hospital, with maintenance treatment of mesalazine 4 g/day accompanied by probiotics.

At the end of July 2016, the patient went to the Institute of Hematology and Blood Diseases Hospital. His hemoglobin level was 109 g/L, with the globulin and the total protein level increasing to 45.7 g/L and 81.9 g/L, respectively. His serum IgG level was 32.3 g/L; M-protein (IgG-λ type) was found by immunoelectrophoresis, accounting for 22.77% of total protein. Free light chain (FLC) examination showed monoclonal gammopathy with free λ levels of 362.5 mg/L, and an involved: uninvolved FLC ratio of 24.17. Repeated bone marrow aspiration and biopsy revealed a diffuse proliferation of dysplastic plasma cells (10%) [Figure 1d and 1f]. Immunohistochemical staining was positive for CD38, CD138, and λ light chains. Flow cytometry evaluation was positive for CD38, CD138, and λ and negative for CD56, CD19, and κ. Fluorescence *in situ* hybridization showed no p53 deletion, 1q21 amplification, RB1 deletion, and immunoglobulin heavy chain gene rearrangement, with no cytogenetic abnormalities detected. The X-ray examination revealed no diffuse osteoporosis. According to the diagnostic standards, he was finally diagnosed as UC with IgG-λ type smoldering multiple myeloma (SMM) in the absence of related symptoms. The patient was discharged from the hospital without accepting any medication for myeloma and a 2-year follow-up of hemoglobin, and M-protein and FLC level showed no obvious progress.

Patients diagnosed with inflammatory bowel syndrome (IBD) are known to be at an increased risk of all kinds of cancers, including hematology malignancies such as leukemia and lymphoma. Some immunology mechanisms exist to explain the association. In chronic inflammatory conditions such as IBD, activated B lymphocytes can induce monoclonal expansion of plasma cells, sometimes resulting in monoclonal gammopathy of undetermined significance (MGUS).[1] Since MM usually develops from MGUS, it is possible that a causal association exists between IBD and MM.[2] In addition, the intestinal mucosal barrier in patients with IBD is often disrupted by inflammatory cytokines such as interleukin (IL)-6, IL-13, and tumor necrosis factor-α,[3] which results in immune response to antigens and activation of B cells and plasma cells. Consequently, patients with IBD are more susceptible to MM and lymphoma.

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Table 1: Diagnosis of smoldering multiple myeloma in the patient

Parameters	Laboratory test results of the patient	Smoldering multiple myeloma reference values[5]
M protein (IgG-λ type)	32.3 g/L	≥30 g/L
Bone marrow plasma cells	10%	≥10%
End-organ damage*	Absent	Absent
Free light-chain ratio	0.040	<0.125 or >8.000
Immunophenotyping	CD56(-), CD19(-), CD38(+)	≥95% BMPC with abnormal phenotype (CD56, CD45/CD19, CD38)
Immunoparesis	Decreased IgA and IgM	Uninvolved immunoglobulins suppression
Cytogenetic abnormalities	None	Del(17p13), t(4;14), 1q21

*End-organ damage: Hypercalcemia, renal disease, anemia, and bone lesions. BMPC: Bone marrow clonal plasma cell.

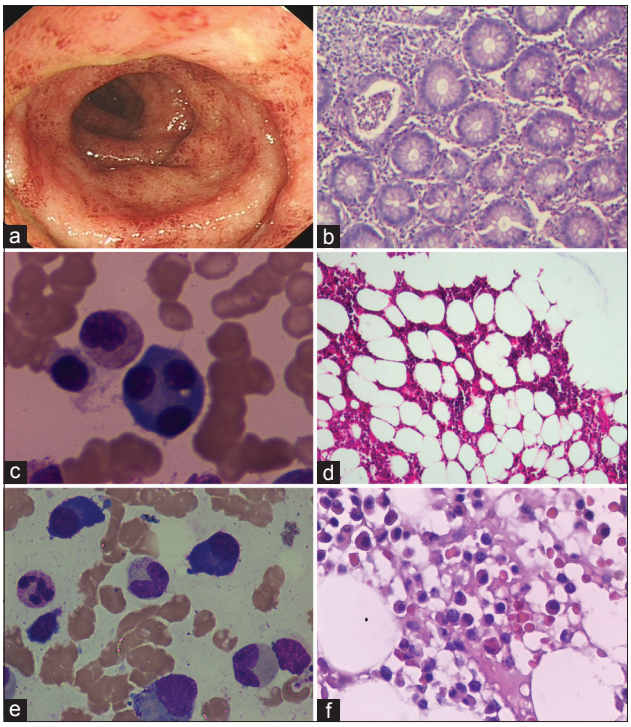

Figure 1: Representative images of the patient. (a) Colonoscopy showed hyperemic mucosa with edema and erosions. (b) Colonoscopy biopsy revealed crypt abscesses and inflammatory cell infiltrations (Hematoxylin and Eosin Staining [H&E], ×100). (c) The first bone marrow aspiration showed 8.5% plasma cells with dysplastic cells (Wright staining, ×100). (d) The first bone marrow biopsy revealed scattered plasma cells (H&E, ×100). (e) Repeated bone marrow aspiration revealed 10% plasma cells with dysplastic cells (Wright staining, ×100). (f) Repeated bone marrow biopsy showed diffuse proliferation of plasma cells (H&E, ×400).

Currently, the standard of care for SMM is observation until progression to symptomatic disease that is defined as end-organ damage. Since high-risk SMM needs strategies to prevent a higher rate of progression, risk stratification for patients is of great significance. The risk factors include FLC ratio (<0.125 or >8.000),[4] bone marrow plasma cells ≥10%, and a serum M protein ≥30.0 g/L. Additional risk factors for progression include immunoparesis with reduction of two uninvolved Ig isotypes, etc. Our patient had bone marrow plasma cells ≥10%, FLC ratio of 0.04, and uninvolved Ig suppression [Table 1]. With several risk factors, he is regarded as high-risk SMM. It has been confirmed that for patients with high-risk SMM, early treatment with lenalidomide plus dexamethasone resulted not only in a benefit in time to progression but also in sustained significant prolongation to overall survival.[6] However, the patient refused any special treatment. Two-year follow-up of hemoglobin, M-protein, and FLC level showed no obvious progress, whereas a long-time follow-up is necessary.

In summary, it is of necessity to have the suspicion of myeloma in patients with IBD, especially those having unexplained anemia, fever, elevated serum protein, and weight loss.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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