Chapter 12
Immunosuppressive Agents and Intestinal Involvement

Kyoko Katakura, Kiyoshi Migita, and Hiromasa Ohira

Abstract Infections, including opportunistic infections, are frequently encountered in clinical practice for rheumatic diseases; such infections represent important complications that can affect the prognosis for survival. While steroids, immunosuppressive agents, and other drugs used to treat them increase the risk of infections, the increased incidences of opportunistic infections associated with the use of biologics have recently been posing a grave concern. In the gastrointestinal tract, cytomegalovirus and candida infections are common and can sometimes be fatal; therefore, it is important that the physician engaged in clinical practice for rheumatic diseases endeavor to detect and treat such infections as early as possible and consistently be aware of complications.

Keywords Opportunistic infection · Cytomegalovirus infection · Candida infection · Steroid · Immunosuppressive agent · Biologics

12.1 Introduction

The onset of rheumatic diseases is underlain by autoimmune abnormalities, and it is also accompanied by functional abnormalities in immunocompetent cells responsible for infection immunity and decreased immune responses to pathogenic microorganisms; the overall incidence of infections is higher in patients

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with untreated rheumatoid arthritis or generalized lupus than in healthy persons. Regarding the actual status of infections in rheumatic disease patients, Falagas et al. reviewed 39 infection-related studies and reported that serious infections developed in 1592 (29%) of 5411 patients examined [1]. Infection risk factors include aging, leukocyte (neutrophil) count reductions, high disease activity, and respiratory and diabetic complications, and steroids, antirheumatic drugs, immunosuppressive agents, and the biologics used to treat them primarily also suppress normal immunity [2, 3]. Therefore, it is important that the attending physician should be fully aware of the associations with the use of these drugs. For example, if at least 95% of glucocorticoid receptors including T cells in living organisms are saturated by a large amount of steroid for a length of time, intense immunosuppression will be induced. In addition, cyclophosphamide, methotrexate, leflunomide, and other drugs suppress immunocompetent cells, such as activated T cells, by suppressing cell cycles; cyclosporin, tacrolimus, and other drugs function by controlling the transcription of IL-2; and TNF-α antibodies and the like promote cytokine neutralization. Furthermore, steroid-immunosuppressive agent combination therapies cause even more intensive immunosuppression, used in opportunistic infections, including tuberculosis, with bacteria, fungi, viruses, protozoans, parasites, and other organisms. Respiratory infections account for more than 50% of cases of infections in rheumatoid arthritis, with the next common sites being skin/soft tissues, gastrointestinal tract/abdominal cavity, urinary tract, and bones/joints [4]. Relatively common gastrointestinal opportunistic infections that can be aggravated to become severe conditions include cytomegalovirus (CMV) infections and candidiasis. In this paper, we overview points to note in the clinical care of these conditions and provide some case presentations. Intestinal tuberculosis is also outlined, bearing in mind that there have recently been increasing reports on extrapulmonary tuberculosis during TNF-α inhibitor treatment.

12.2 Cytomegalovirus Infections

While cytomegalovirus (CMV) occurs as an asymptomatic infection in approximately 90% of adult Japanese people, it can become reactivated in immunosuppressed states and result in a wide variety of organ and tissue disorders. Although CMV is distributed widely in the gastrointestinal tract, it commonly occurs in the large intestine, and it can also be found in the esophagus, stomach, and duodenum. The esophageal CMV lesions are accompanied by odynophagia and the large intestine CMV lesions, by abdominal pain, pyrexia, diarrhea, bloody stools, and other symptoms. The characterization of CMV ulceration is that the ulcer often exhibits a morphology with no surrounding elevation and the ulcer margin abruptly drops onto the ulcer base and is hence the term “punched-out ulcers.” Histologically, intranuclear

inclusion bodies are found in glandular epithelial cells, fibroblasts, and vascular endothelial cells. Because CRP elevations are not always present in the initial stage of CMV infection, a CMV antigenemia (CMV-Ag) method using an antibody against the 65-kd lower-matrix phosphoprotein (pp65), which is a CMV structural protein appearing in the early stage of CMV infection, is useful in diagnosing the disease. To establish the diagnosis of CMV gastroenteritis, it is necessary to take a biopsy from a gastrointestinal ulcer or erosion to demonstrate the presence of the virus in the tissue. It is treated with ganciclovir administered at a dose of 5 mg/kg twice a day for 14 days and then at a maintenance dose of 5 mg/kg in reference to CMV-Ag. This treatment necessitates dose adjustments in patients with impaired renal function.

12.2.1 Patient 1

A woman in her 60s, with rheumatoid arthritis onset at 40 years of age, had been treated with methotrexate and prednisolone 2.5 mg, also anti-TNF-α antibody therapy added 4 years before this admission.

In early February 2014, she experienced pharyngalgia and general malaise and was admitted to a nearby hospital. The lab results showed anemia and thrombocytopenia with a hemoglobin level of 8.8 g/dL and a platelet count of 21,000, as well as an increased inflammatory reaction with a CRP level of 10 mg/dL. The suspected diagnosis was disseminated intravascular coagulation (DIC), and thus she was treated with a protease inhibitor with methylprednisolone (250 mg for 3 days), and then the dose was tapered to prednisolone 30 mg. In late February, tarry stools occurred, and the Hb level decreased to 3.4 g/dL; she was transferred to our hospital for extensive examination and treatment. On admission, the CMV-Ag level was high at 202; thrombocytopenia due to cytomegalovirus infection was suspected, and ganciclovir was started at a dose of 500 mg. Upper gastrointestinal endoscopy detected many large circular punched-out ulcers in the gastric antrum (Fig. 12.1), and an ulcer biopsy revealed a positive test for CMV (Fig. 12.2). Melena was found to be attributable to bleeding from CMV infection ulcer, and anemia was ameliorated after treatment.

12.3 Candida Infections

Candidiasis is normally an endogenous infection with candida occurring commonly in the patient's oral cavity, gastrointestinal tract, vagina, skin, and other parts of the body. In immunosuppressed states associated with collagen disease treatment, esophageal candidiasis and deep candidiasis can develop, causing odynophagia and

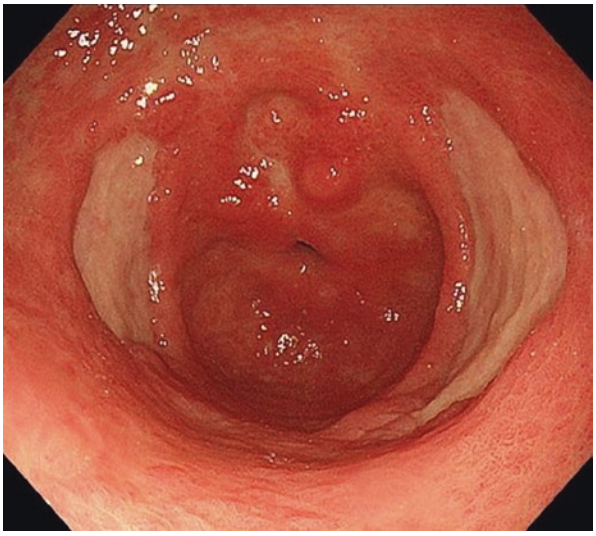

Fig. 12.1 Endoscopy of the stomach. Large clearly margined circular punched-out ulcers are seen in the anterior and posterior walls of the gastric antrum

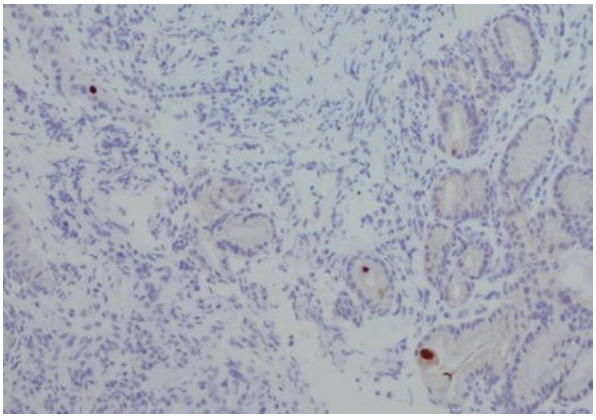

Fig. 12.2 Histopathology of the stomach. Immunological staining of a biopsy from the ulcer base shows the sporadic presence of CMV-positive cells

heartburn. It is known that immediately after steroid pulse therapy, systemic dissemination of fungal infections and acute exacerbation of fungal pneumonia are not rare. Therefore, if the presence of a white film on the tongue, or endoscopically observed gastrointestinal mycosis, or elevated serum β-D glucan levels is noted, administration of antifungal drugs such as itraconazole is desirable. In esophageal candidiasis, endoscopy reveals a millet to rice grain-size white film adhering to the esophagus sporadically or in the form of a band, which cannot be washed off.

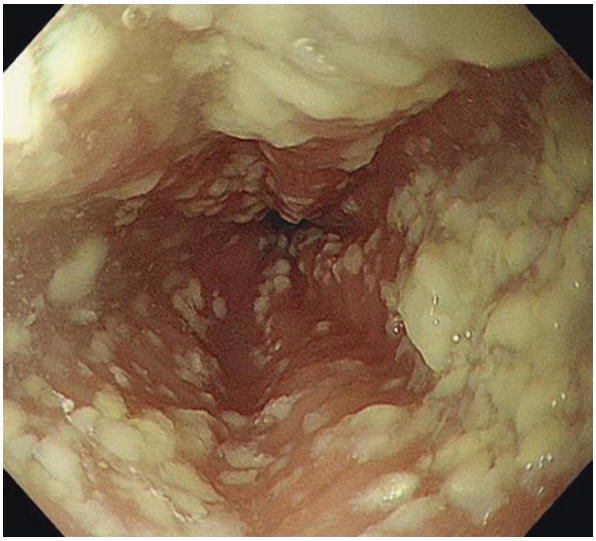

Fig. 12.3 Endoscopy of the esophagus. A thick, slightly elevated, longitudinally fused white film is seen adhering to the esophagus

Although the classification of Kodsi et al. [5] is used for the endoscopic classification, mucosal states are difficult to examine because of extensive coverage by a white film in severe cases. The oral cavity and esophagus can serve as entrances to the host in systemic infections with candida and other fungi, and early treatment initiation is desirable; therefore, for oral candidiasis if noted, treatment with amphotericin B gargling and swallowing is recommended.

12.3.1 Patient 2

A woman in her 60s, who had been diagnosed with dermatomyositis 12 years previously, experienced interstitial pneumonia and started treatment with prednisolone at a dose of 60 mg/day and cyclosporin at 100 mg/day. She experienced repeated recurrences and exacerbations upon steroid dose reductions, which were treated by a switch to steroid pulse therapy and tacrolimus; she was then followed up with Medrol 12 mg and tacrolimus 3 mg.

In early April of 2018, she experienced a strange sensation of the pharynx and epigastric pain and difficulty with oral food intake. Her serum albumin level was 2.1 g/dL, suggesting advanced undernutrition; thus, she was admitted to hospital in mid-May. Upper gastrointestinal endoscopy revealed a thick, slightly elevated, longitudinally fused, white film adhering to the esophagus (Fig. 12.3), showing a finding of candidal esophagitis. In addition, clearly margined circular punched-out

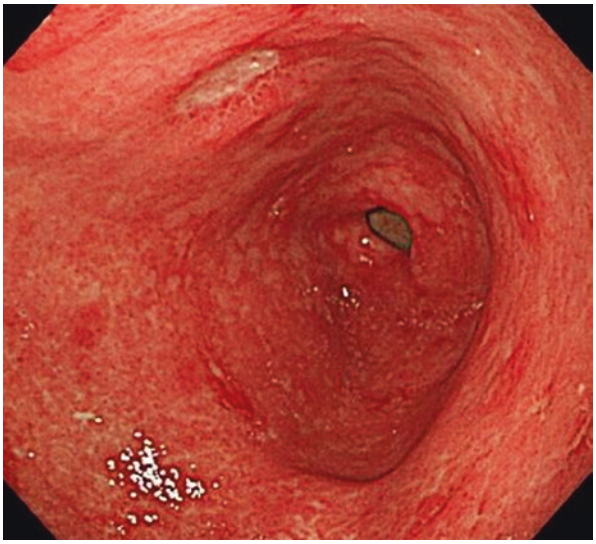

Fig. 12.4 Endoscopy of the stomach. Clearly margined circular punched-out ulcers are seen in the anterior wall of the gastric antrum

ulcers were found in the gastric antrum (Fig. 12.4), and an ulcer biopsy revealed a positive test for CMV. Oral miconazole was started, resulting in gradual amelioration of symptoms.

12.4 Intestinal Tuberculosis

Japan is ranked high in the incidence of tuberculosis among the developed countries; the incidence is more than two times higher, at 20.6 patients per 100,000 people in Japan, than in Europe and the United States (10 patients per 100,000 people). Since the use of TNF inhibitors for rheumatoid arthritis increases the risk of tuberculosis, importance should be placed on screening and prophylaxis when biologics are started. A majority of cases of onset of tuberculosis during TNF inhibitor treatment occur as a result of reactivation of latent tuberculosis infection. It is recommended that a comprehensive judgment be made based on interviews, tuberculin reactions, and interferon-gamma release assays (IGRAs), such as T-SPOT, chest radiography, CT scans, and other findings prior to the start of treatment, and that isoniazid be administered at a dose of 300 mg/day for 6–9 months starting 3 weeks before the start of treatment.

In typical tuberculosis infections, extrapulmonary tuberculosis accounts for not more than 20% of all cases affected; about 50% of patients with tuberculosis developing during TNF inhibitor treatment are affected by extrapulmonary tuberculosis [6], which includes intestinal tuberculosis. Although most cases of

intestinal tuberculosis are considered to be disseminated intraductally by sputum and swallowing containing *Mycobacterium tuberculosis*, the absence of active tuberculosis in the lungs is not rare. The most common site is the ileocecum, followed by the lower part of the jejunum and the ileum. Lesions originate from lymph follicles and form ulcers and can subsequently produce stenosis with the cure of ulcers, which may be accompanied by abdominal pain, diarrhea, abdominal distention, pyrexia, and other symptoms. It is diagnosed if one of the diagnostic criteria is met: (1) demonstration of *M. tuberculosis* or caseating granuloma by open biopsy, (2) demonstration of *M. tuberculosis* by biopsy tissue culture, (3) radiographic/endoscopic findings characteristic of intestinal tuberculosis and amelioration of the findings by antituberculotic therapy, and (4) demonstration of *M. tuberculosis*-specific genome by biopsy tissue PCR. As with pulmonary tuberculosis, the basic treatment comprises a 2-month course of 4-drug treatment with rifampicin, isoniazid, pyrazinamide, and streptomycin, followed by a 4-month course of 2-drug treatment with rifampicin and isoniazid, or a 3-drug treatment with these two drugs and ethambutol.

12.5 Conclusion

Since new biologics have been increasingly approved with indications of rheumatic diseases, countermeasures against opportunistic infections remain important. Since gastrointestinal lesions can help diagnose opportunistic infections and are sometimes fatal due to bleeding and perforations, they must be diagnosed quickly and accurately. To this end, a comprehensive understanding in this field is essential.

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