Case Report
Autoimmune neutropenia preceding Helicobacter pylori-negative MALT lymphoma with nodal dissemination

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Abstract: Autoimmune neutropenia (AIN), resulting from granulocyte-specific autoantibodies, is much less frequent than other autoimmune hematologic disorders including autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP). These autoimmune disorders may precede, synchronize, or follow collagen disorders, viral infections, and lymphoid neoplasms. Herein we present the first case of AIN in association with Helicobacter pylori-negative mucosa-associated lymphoid tissue (MALT) lymphoma with nodal dissemination. In our case, AIN, accompanied by ITP, occurred prior to the clinical manifestation of lymphoma. AIN and ITP were well managed afterwards, but they relapsed in accordance with the recurrence of lymphoma. The administration of prednisolone at 0.5 mg/kg daily alleviated the cytopenias within a week. In general, combination chemotherapy is performed for the treatment of lymphoma-associated autoimmune hematologic disorders and indeed seems to be effective. Our case indicates that corticosteroid monotherapy may be effective for lymphoma-associated AIN especially when AIN precedes the onset of lymphoma.

Keywords: MALT lymphoma, autoimmune neutropenia, immune thrombocytopenia, corticosteroid, combination chemotherapy

Introduction

Autoimmune hematologic disorders such as autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) are commonly seen in patients with lymphoproliferative neoplasms [1]. The prevalence rates of AIHA and ITP in B-chronic lymphocytic leukemia (B-CLL) are identified as 5-10% and 1-5%, respectively [2]. Hematologic disorders in association with other lymphoid malignancies are less frequent. AIHA and ITP were recorded in 1.6% and 0.8% of patients with non-Hodgkin lymphomas (NHLs) excluding B-CLL, respectively [3]. In Hodgkin lymphoma, the prevalence rates of AIHA and ITP were identified as 0.2% and 1.0%, respectively [4]. These autoimmune hematologic disorders may precede, synchronize, or follow the clinical manifestation of lymphoid malignancies. Management of the underlying lymphoid malignancies is crucial for successful treatment of AIHA or ITP. To this end, combination chemotherapy for advanced disease and surgical resection for localized disease are the reasonable treatment options, which are effective for more than a half of the patients [3, 5]. In recent years, rituximab has also been shown to exhibit a durable and favorable efficacy against AIHA in association with B-CLL [6]. On the other hand, there are no comprehensive data on the efficacy of steroid monotherapy which is usually administered for idiopathic autoimmune disorders.

Autoimmune neutropenia (AIN) is much less frequently seen in patients with lymphoproliferative neoplasms than AIHA or ITP. It has mostly been documented in case studies and its treatment strategy has not been well established. Here, we describe the first case of AIN plus ITP...
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Preceding Helicobacter pylori-negative mucosa-associated lymphoid tissue (MALT) lymphoma with nodal dissemination.

**Case report**

A 31-year-old previously healthy woman visited another institution with a 5-day history of chills, purpura, and oral hemorrhage. Laboratory data showed bicytopenia with white blood cell (WBC) count of $1.9 \times 10^9/L$, neutrophil count of $0.1 \times 10^9/L$, and platelet count of $28 \times 10^9/L$. The bone marrow was slightly hypercellular without excessive blasts or dysplastic changes, suggesting autoimmune mechanisms as the cause of cytopenias. While granulocyte-colony stimulating factor (G-CSF) was ineffective for neutropenia, prednisolone at an initial dose of 2 mg/kg daily improved both neutropenia and thrombocytopenia. Her symptoms faded away, and thus prednisolone was tapered and stopped. One year later, her platelet count dropped below $10 \times 10^9/L$ and prednisolone was resumed. Neutropenia with the minimum neutrophil count of $0.0 \times 10^9/L$ was also identified irrelevantly to the platelet count. Careful observation with prednisolone at 5-10 mg daily was continued. At the age of 35 years, the recurrence of the cytopenias was recorded again with WBC count of $0.9 \times 10^9/L$ with 5% neutrophils and platelet count of $< 5 \times 10^9/L$. Bone marrow aspiration showed a normocellular marrow with increased megakaryocytes. Antibodies against neutrophils and platelet glycoprotein IIb/IIIa were positive, leading to the diagnosis of AIN and ITP. She underwent prednisolone at 30 mg (0.5 mg/kg) daily, which was augmented by intravenous immunoglobulin for five consecutive days. While this strategy was effective for AIN, the recovery of platelet count was transient. Thus, a laparoscopic splenectomy was performed to treat the refractory ITP. The initial post-operative WBC and platelet counts were $11 \times 10^9/L$ and $112 \times 10^9/L$, respectively. Histopathological examination of the spleen did not reveal any infiltration of lymphoma. Four years later, at the age of 39 years, prednisolone was discontinued without a recurrence of the cytopenias.

Since the age of 36 years, she had complained of mild enlargement of her left submandibular gland. At the age of 42 years, the patient presented to our hospital with submandibular gland enlargement and cervical lymphadenopathy in the absence of B symptoms. Laboratory tests were almost unremarkable except for serum interleukin-2 receptor (sIL-2R) level of 1,311 U/mL. There was no evidence of Helicobacter pylori infections. F-18 fluorodeoxyglucose-positron emission tomography (FDG-PET) combined with computed tomography (CT) scan showed uptakes in the submandibular glands and generalized lymph nodes. Excisional biopsy of a left submandibular gland was performed and histopathological study revealed proliferation of small to medium-sized atypical centrocyte-like lymphoid cells with lymphoplasmacytic differentiation. Immunophenotype of the lymphoid cells was CD20+, CD79a+, CD5-, and CD10- (Figure 2A). Immunoglobulin light chain restriction was noted (Figure 2B). Fluorescence in situ hybridization analysis did not detect API2/MALT1 fusion signals. Bone marrow biopsy did not reveal infiltration of lymphoma cells. Comprehensive, the patient was diagnosed as Helicobacter pylori-negative MALT lymphoma (Ann Arbor clinical stage, IIIA) with nodal dissemination. Treatment was exerted with rituximab administered at 375 mg/m² weekly for four consecutive weeks, which resulted in a

![Figure 1](image)

**Figure 1.** Clinical course of the present case. AIN, autoimmune neutropenia; ITP, immune thrombocytopenia; PSL, prednisolone.
salient regression of the affected sites and a normal serum sIL-2R level.

Twelve months after the completion of rituximab monotherapy, a follow-up laboratory test recorded a gradual but steady increase in serum sIL-2R level. The patient then presented with severe menorrhagia due to thrombocytopenia, which was followed by neutropenia. The cytopenias were transient and spontaneously

Figure 2. MALT lymphoma with nodal dissemination. A. Microscopic examination of an excised submandibular gland indicated proliferation of small to medium-sized lymphoid cells (H-E stain). B. The lymphoid cells were positively stained with anti-CD20 antibody. C. Immunohistochemical study revealed immunoglobulin light chain restriction (λ > κ). D. F-18 fluorodeoxyglucose-positron emission tomography showed uptakes in cervical, supraclavicular, axillary, mediastinal, and abdominal (paraaortic and iliac) lymph nodes as well as submandibular glands.
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Ameliorated. F-18 FDG-PET/CT scan demonstrated the recurrence of nodal lesions (Figure 2D). Finally, she was repeatedly affected by severe cytopenias with neutrophil count of 0.1 $\times$ 10$^9$/L and platelet count of 5 $\times$ 10$^9$/L. Her platelet-associated immunoglobulin G level was 123 ng/10$^7$ platelets (reference range, 9-25 ng/10$^7$ platelets). There was no evidence of active collagen disorders or infections, and there were no causative drugs. Taken together, the patient was diagnosed with the relapse of AIN plus ITP which was triggered by recurrent MALT lymphoma. Since she declined to receive immunotherapy for family reasons, treatment was commenced with oral prednisolone at 30 mg (0.5 mg/kg) daily. G-CSF was not administered. Both neutrophil and platelet counts were thoroughly recovered within one week. Because of another recurrence of thrombocytopenia when the daily prednisolone dose was tapered to 5 mg, the patient has been administered a maintenance prednisolone dose of 7 mg daily for the following eight months. MALT lymphoma showed a slight regression after steroid therapy but remained persistent.

Discussion

AIN is defined as neutropenia resulting from increased destruction of neutrophils by antibodies directed against cell surface antigens [7]. The diagnosis of AIN is based on evidence of these antineutrophil antibodies. There are several methods to detect serum antineutrophil antibodies including agglutination, cytotoxicity, direct and indirect immunofluorescence, direct and indirect antiglobulin assays, and tests that use binding of staphylococcal protein A to surface immunoglobulins. These assays are not routinely performed due to technical difficulties. AIN is classified into primary (idiopathic) AIN and secondary AIN. Primary AIN is usually found in newborn infants with an incidence of 1/100,000. Secondary AIN is more commonly seen in adults. Underlying causes of secondary AIN include collagen disorders, viral infections, and lymphoproliferative neoplasms, among which systemic collagen disorders are the most frequent. Similar to AIHA and ITP, secondary AIN may precede, synchronize, or follow the underlying disorders. Secondary AIN is usually accompanied by AIHA and/or ITP, and only occasionally manifest as isolated neutropenia.

In a retrospective study of Hodgkin lymphoma with AIN, four (80%) of five cases were found to have concurrent AIHA, Evans syndrome, or aplastic anemia [8]. To our knowledge, ours is the first case of AIN associated with Helicobacter pylori-negative MALT lymphoma. AIN was accompanied by ITP and preceded the clinical manifestation of lymphoma. Our case also suggests that the aggravation of lymphoma induced the relapse of autoimmune hematologic cytopenias.

Treatment for the underlying disorders is believed to be crucial for improvement in secondary AIN, similar to the management of secondary AIHA or ITP. Thus, therapies against the underlying neoplasms are preferred in the treatment of lymphoma-associated AIN. For instance, in two cases of Hodgkin lymphoma with AIN, neutrophil count recovered after combination chemotherapy with corticosteroids and cyclophosphamide (± vincristine) [7]. Nakabe et al. reported a case of diffuse large B-cell lymphoma complicated by isolated AIN [9], where combination chemotherapy was effective for both lymphoma and secondary neutropenia whereas G-CSF resulted in a transient recovery of neutrophil count. Gupta et al. described a case of isolated AIN preceding H. pylori-associated gastric MALT lymphoma [10]. In Gupta's case, recovery of neutrophil count was noted shortly after eradication therapy. It is controversial whether the neutropenia of the case was induced by MALT lymphoma or H. pylori infection. Our case is featured by sensitivity of AIN plus ITP to corticosteroids. Prednisolone at 0.5 mg/kg daily was effective for neutropenia within one week. There is a similar case study of Hodgkin lymphoma with isolated AIN in which neutrophil count recovered within 48 hours after initiation of corticosteroid therapy [8]. Although corticosteroid monotherapy is not widely approved, it can immediately improve lymphoma-associated AIN under some circumstances and therefore should be considered as a treatment option. Intriguingly, corticosteroid monotherapy is effective for ITP preceding NHL while it does not usually deliver a durable response to ITP occurring at or after diagnosis of NHL [3]. It is therefore plausible that AIN preceding NHL may also respond well to corticosteroid monotherapy. Accumulation of further case reports are required to confirm this theory.
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Disclosure of conflict of interest

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