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A Case of Non-Hodgkin's Lymphoma Following Long-Term Corticosteroid Therapy for Addison's Disease

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Abstract: A 76-year-old Japanese woman had suffered from fatigue, weight loss, and cutaneous hyperpigmentation at the age of 38 years and was diagnosed as having tuberculous Addison's disease. Since then, corticosteroids had been administered effectively as hormonal replacement. At the age of 75 years, the patient presented with a progressive, painless swelling in the left eyelid due to an ill-defined tumor of rubbery consistency in the superotemporal aspect of the orbit. Computed tomography, magnetic resonance imaging, and scintigraphy revealed a wide distribution of tumors, but not in the adrenal gland, which led to the suspicion of systemic malignant lymphoma. Histopathologic examination of the excised orbital tumor was compatible with non-Hodgkin's lymphoma of the B-cell type. We believe this is the first report of Addison's disease presenting with non-Hodgkin's lymphoma. This disease process was characterized by the development of a lymphoid malignancy after long-term corticosteroid therapy to control the adrenal insufficiency, and by the widespread involvement of the lymph nodes and orbit but not the adrenal gland. Corticosteroid-induced abnormal immune state was considered to be the pathogenesis of this unusual complication. **Jpn J Ophthalmol 1998;42:393–397**

Key Words: Addison's disease, corticosteroid, immunosuppression, non-Hodgkin's lymphoma, orbit.

Introduction

Addison's disease is a chronic systemic disease resulting from an adrenal insufficiency, and is characterized by weakness, weight loss, hypotension, irritability, gastrointestinal disturbance, and cutaneous hyperpigmentation. Before the antibiotic era, its principal cause was a tuberculous infection of the adrenal gland. In recent years, the cause of the disease has changed in developed countries so that idiopathic or autoimmune disease outnumbers adrenal tuberculosis. Chronic thyroiditis, rheumatoid arthritis, and Sjögren's syndrome are frequent complications that are attributable to the immune-mediated pathomechanisms.[1,2] Although primary malignant lymphoma involving the adrenal gland is not uncommon, Addison's disease with concurrent adrenal lymphoma has been rarely reported.[3–18] We describe herein a patient with tuberculous Addison's disease who had maintained adrenal function with long-term corticosteroid therapy and subsequently developed systemic non-Hodgkin's lymphomas (NHL) including in the orbit but not in the adrenal gland. We shall discuss the pathogenesis of NHL as a possible complication based on the current immunosuppressive theory on the etiology of malignant lymphoma.

Case Report

A 76-year-old Japanese woman was referred to us for investigation of an eyelid tumor. She was diagnosed with pulmonary tuberculosis in the fourth decade of life, and was treated with antibiotics. At 38 years of age, she suffered fatigue, weight loss, and hyperpigmentation of the skin and mucous membranes, and was diagnosed as having Addison's dis-

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ease. Oral corticosteroids were prescribed and continued in the following years, with a recent dose of prednisolone 5 mg per day that had effectively relieved symptoms and hyperpigmentation. Several months before presentation, she first noted a progressive, painless swelling in the left upper eyelid.

On presentation, the patient appeared well on physical and skin examinations. A smooth-surfaced mass with rubbery consistency and measuring 3.0 mm × 2.0 mm in size was palpable beneath the left eyelid (Figure 1). Best visual acuity was RE: 0.4 and LE: 0.5 with moderate myopic correction. The anterior segments, media, and fundi were unremarkable except for moderate cataracts. Laboratory studies showed mild anemia and elevated levels of the lactic dehydrogenase and enolase. Results of endocrinologic examination were also normal, with normal levels of serum electrolytes, cortisol, and ACTH. Infection by Epstein-Barr virus was not tested. Computed tomography (CT) scan revealed mass lesions in the left axilla and left elbow but not in the adrenal glands. In addition, an ill-defined, monomorphous isodensity tumor was present in the preseptal, superotemporal aspect of the orbit, which had no bone erosion (Figure 2). T1-weighted magnetic resonance (MR) orbital images showed a mass of moderate signal intensity without encapsulation and T2-weighted images showed a homogeneous mass of high signal intensity. Noticeably, CT or MR scans of the adrenal glands were unremarkable. Whole body scintigraphy using 67Ga disclosed distinct tracer with widespread uptake by organs including the left orbit, left axilla, anterior mediastinum, left elbow, and right colon, but no uptake by the adrenal glands. Thus, these clinical and imaging studies led us to suspect systemic lymphoma, but the patient did not consent to a diagnostic biopsy.

The orbital mass enlarged during the subsequent follow-up of 2 months. Surgical treatment of the tumor was performed, and because an intraoperative biopsy revealed a possible malignancy, an extensive excision was carried out. Histopathologic examination with hematoxylin-eosin stain showed that the tumor was filled with many medium-sized and occasionally large-sized, lymphoid cells containing irregular-shaped nuclei (Figure 3A). This led to a histopathologic diagnosis of non-Hodgkin's malignant lymphoma. The neoplastic cells demonstrated distinct immunoreactivities to B-cell markers, CD-20, L26, MX-panB and MB-1, and not to T-cell markers, UCHL1, CD3, CD4, and CD8 (Figure 3B).

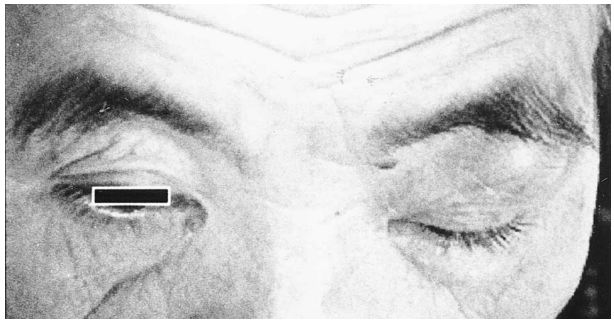

Figure 1. Swelling of left upper eyelid due to orbital malignant lymphoma.

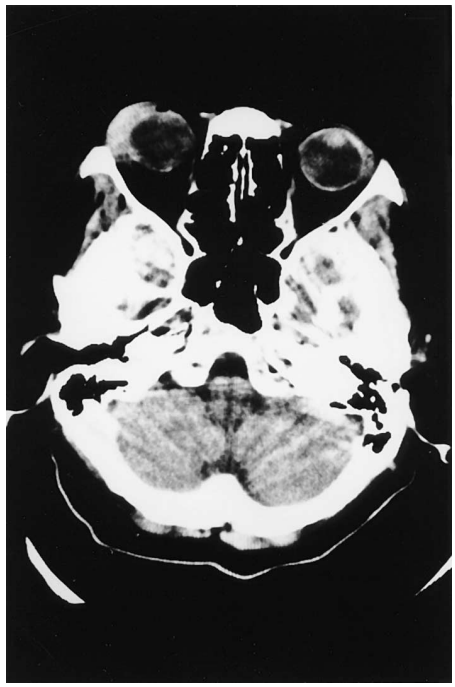

Figure 2. Computed tomography scan revealing mass lesion in superotemporal aspect of left orbit.

Discussion

In a recent survey of patients with Addison's disease in England, a total of 86 were identified between 1987 and 1993, and 81 (93%) were attributed to autoimmune destruction of the adrenal cortex, and none was attributable to tuberculosis.[1] A nationwide survey in Japan showed that 74 new cases were diagnosed between 1987 and 1991, of which, 36 cases (48.6%) were regarded as autoimmune-mediated disease and 28 (37.8%) as adrenal tuberculosis, indicating a still relatively high incidence of tuberculous Addison's disease.[2] Although the adrenal gland is usually involved in malignant lymphoma, it is rare for adrenal lymphoma to cause adrenal insufficiency

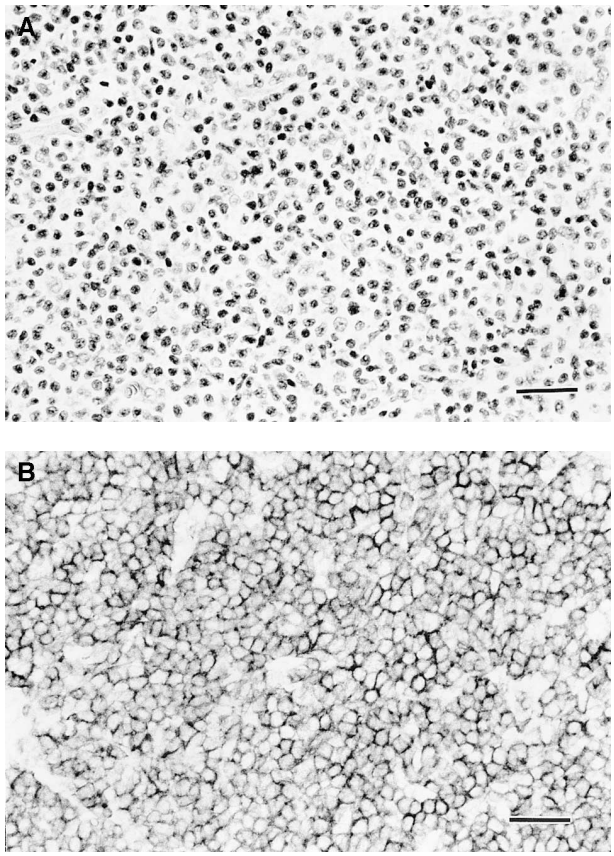

Figure 3. (**A**) Histopathology of excised tumor specimen illustrating diffuse proliferation of lymphomatous cells. Hematoxylin and eosin staining. Bar = 40 μm. (**B**) Histochemistry of tumor cells with anti-CD20 monoclonal antibody illustrating positive immunoreactivities. Bar = 40 μm.

or Addison's disease. Our search of the English and Japanese literature using the MEDLINE database between 1983 and 1997 revealed only 16 cases of primary adrenal lymphoma presenting as Addison's disease. These cases were mostly NHL confined to the adrenal glands bilaterally and showed hormonal insufficiency and concurrent adrenal malignancy.[3–18]

Our patient is unusual in many respects; the NHL occurred many years after the onset of Addison's disease, and adrenal function had been controlled until the development of the lymphoma. The NHL was systemic but did not involve the adrenal gland. There has been, to the best of our knowledge, no previous report of a similar case. Thus, whether the development of malignant lymphoma represents a meaningful association with Addison's disease or is merely a coincidence warrants additional discussion. In view of the long maintenance of adrenal function. it is likely that this association is not directly related to Addison's disease itself but attributable to an alteration in the immune state due to long-term corticosteroid therapy.

Clinical and epidemiologic evidence has been accumulated to suggest that lymphoid malignancies such as NHL are associated with an abnormal immune state. Organ transplant recipients who receive immunosuppressive therapy have a substantially higher risk of NHL than the general population; in a multicenter study of a large series of patients, the incidence of NHL was 101 of 45,141 kidney transplant patients (versus 2.7 expected in the general population) and 93 of 7,634 heart transplant recipients (versus 0.6 expected). It was suggested that the risk of NHL is related to the aggressiveness of the immunosuppressive regimen.[19] Lymphomas associated with human immunodeficiency virus have become an increasing problem, as patients with AIDS have a high risk of developing NHL.[20] Autoimmune diseases or chronic inflammatory disorders have also been suggested to be linked with a higher risk of NHL in patients receiving immunosuppressive medications. The occurrence of NHL is the most serious complication of Sjögren's syndrome and rheumatoid arthritis; a cohort study in Finland of 676 patients with primary Sjögren's syndrome and 9,469 with rheumatoid arthritis revealed the standardized incidence ratio of NHL to be 2.2 and 4.5, respectively, indicating a higher risk for both as compared with that in the general population.[21] Another study showed that 3 of 30 patients with primary Sjögren's syndrome had malignant lymphoma, whereas none of the 56 patients with isolated keratoconjunctivitis sicca had lymphomas.[22] Furthermore, many reports have emphasized the close association between NHL and chronic inflammatory disorders, including systemic lupus erythematosus, dermatomyositis, Hashimoto's thyroiditis, and sarcoidosis.[23–26] Of a cohort of 1,585 patients with systemic lupus erythematosus, 8 cases were affected with NHL, showing a significant excess of relative risk for lymphoid malignancy.[27]

The distinct association of lymphoid malignancies, namely NHL, with various disorders may involve multiple factors that include congenital or acquired immune defects, drug-induced immunosuppression, genetic predisposition, and latent infection with prooncogenic virus, such as Epstein-Barr virus and herpes zoster virus type 6.[28] It is significant in this connection that the patient described here developed systemic NHL after long-term administration of corticosteroids, suggesting that the development of NHL is an insidious complication of immunosuppression.

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Several case reports are relevant to this explanation, which described malignant lymphoma following corticosteroid therapy for various diseases. Jacobs et al[29] reported a 45-year-old man who presented with multiple aneurysm formation, which entailed long-term corticosteroid therapy, and later developed lymphoma. Pennisi et al[30] described a patient with adult T-cell leukemia who developed epidural NHL following corticosteroid administration. Real et al[31] reported a 38-year-old homosexual man with Burkitt's-like lymphoma who was treated with a high dose of corticosteroid for 3 weeks and developed systemic Kaposi's sarcoma, which regressed completely with withdrawal of chemotherapy and corticosteroid therapy. Mori et al[32] described a 70-year-old man with chronic progressive pulmonary fibrosis who was given a high dose of corticosteroid for 1 year and subsequently presented with malignant lymphoma of the orbit.

With reference to the current view on the etiology of malignant lymphoma, it is most likely that the underlying etiology of the NHL in the present case is attributable to the abnormal immune state due to long-term corticosteroids. This case illustrates an additional example that corticosteroid-induced immunosuppression may increase the risk of NHL.

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