CASE REPORT

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Orbital lymphoma with isolated occult bilateral adrenal involvement: report of an extremely rare case

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Abstract

Orbital lymphoma is very rare malignant neoplasm, usually diagnosed in early stage of disease as primary lymphoma, but dissemination occurs in approximately 33% of cases. Isolated bilateral adrenal lymphomatous involvement is extremely rare, described in 0.83% of cases. We present autopsy case of a 63-year-old man with bilateral orbital diffuse large cell lymphoma, clinical stage IEA, successfully treated by one cycle of chemo- and radiotherapy, but after administration of the second cycle, the patient developed signs of gastrointestinal hemorrhage and died two months after the diagnosis. Autopsy findings exclude lymphoma involvement of any organ except histopathological infiltration of both adrenal glands without evidence of a mass lesion.

Keywords: extranodal lymphoma, orbital lymphoma, adrenal lymphoma, autopsy.

Introduction

Orbital lymphoma (OL) is very rare malignant neoplasm, comprising only 1% of all non-Hodgkin's lymphomas (NHL) [1] and 5–14% of all extra-nodal lymphomas [2]. It is usually diagnosed in early stage of disease as primary lymphoma, but dissemination occurs in approximately 33% of cases [2]. Bilateral OL is observed in 7% to 24% of patients [2, 3]. The predilection for site of extra-orbital disease was described: lymph nodes 29%, skin 13%, bone marrow 8%, spleen 6%, temporalis fossa 5%, salivary gland, sinuses and lung 4% each and other organs less than 3% [3]. Isolated bilateral adrenal involvement is extremely rare, described in 0.83% of cases [4].

In this article, we present autopsy case of a 63-year-old man with bilateral orbital diffuse large cell lymphoma, with isolated occult bilateral adrenal involvement.

Case presentation

A 63-year-old man with no previous history of chronic disease or malignancy presented with slowly enlarging painless lesions of both orbits, with proptosis and ocular adnexal soft tissue swelling with eyelid ptosis, proptosis and livid discoloration of both eyelids of eight months duration. These symptoms were associated with headaches and fatigue. His family history was noncontributory. He was admitted to Clinic for Ophthalmology for further diagnosis of an orbital lesion. A magnetic resonance imaging (MRI) scan of endocranium showed deep orbital tumor of the right side and deep orbital and eyelid infiltration of the left side, without extra-orbital involvement. Right chronic pansinusitis was also presented. Diagnosis was obtained by incisional biopsy of the left orbital tumor. A histopathological analysis of tumor showed diffuse and dense eyelid infiltration by uniform population of blue round neoplastic cells (Figure 1A). The neoplastic cells are middle-sized and large lymphoid cells with scant cytoplasm, large nuclei, with one to three peripherally positioned nucleoli (centroblasts and rare immunoblasts) with scattered small non-neoplastic lymphocytes (Figure 1B). A histopathological analysis with immunohistochemistry of the tumor specimen confirmed the presence of non-Hodgkin's lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), centroblastic, germinal center (GC) subtype, with CD20 (Figure 1C) and CD10 positivity (Figure 1D) and a moderate proliferative index (50% of tumor cells were Ki-67 positive) (Figure 1E). Tumor cells were negative for CD3, CD5, Bcl-2, Bcl-6 (Figure 1F), MUM-1 (Figure 1G), CD23, CD43 and cyclin D1.

The patient was admitted to Clinic for Hematology for staging and therapy purpose. The patient was afebrile, without "B" symptoms. Examination revealed *Eastern Cooperative Oncology Group* (ECOG) Performance Status 1, normal blood pressure, no lymphadenopathy and no hepatosplenomegaly. Electrocardiogram showed no signs of acute coronary syndrome or arrhythmia. Complete blood count was in the normal reference ranges (hemoglobin 141 g/L; 8.6×10^9 leukocytes/L; and 191×10^9 platelets/L). Other laboratory tests revealed the following: erythrocyte sedimentation rate 24 mm/h, fibrinogen 59.9 mg/dL, prothrombin time (PT) 107%, partial thromboplastin time (PTT) 24 s, C-reactive protein (CRP) 19.20 mg/L, β_2-microglobulin 3.92 mg/L, normal level of immunoglobulins (IgG 12.10 g/L, IgA 1.42 g/L, IgM 0.69 g/L), albumin 38 g/L,

serum lactate dehydrogenase level was normal (471 U/L), alanine aminotransferase (ALT) 36 U/L, aspartate aminotransferase (AST) 167 U/L, γ-glutamyltransferase (GGT) 117 U/L, blood glucose 5 U/L, α-amylase 46 U/L, urea 5.9 mmol/L, creatinine 90 μmol/L. All virological tests were negative.

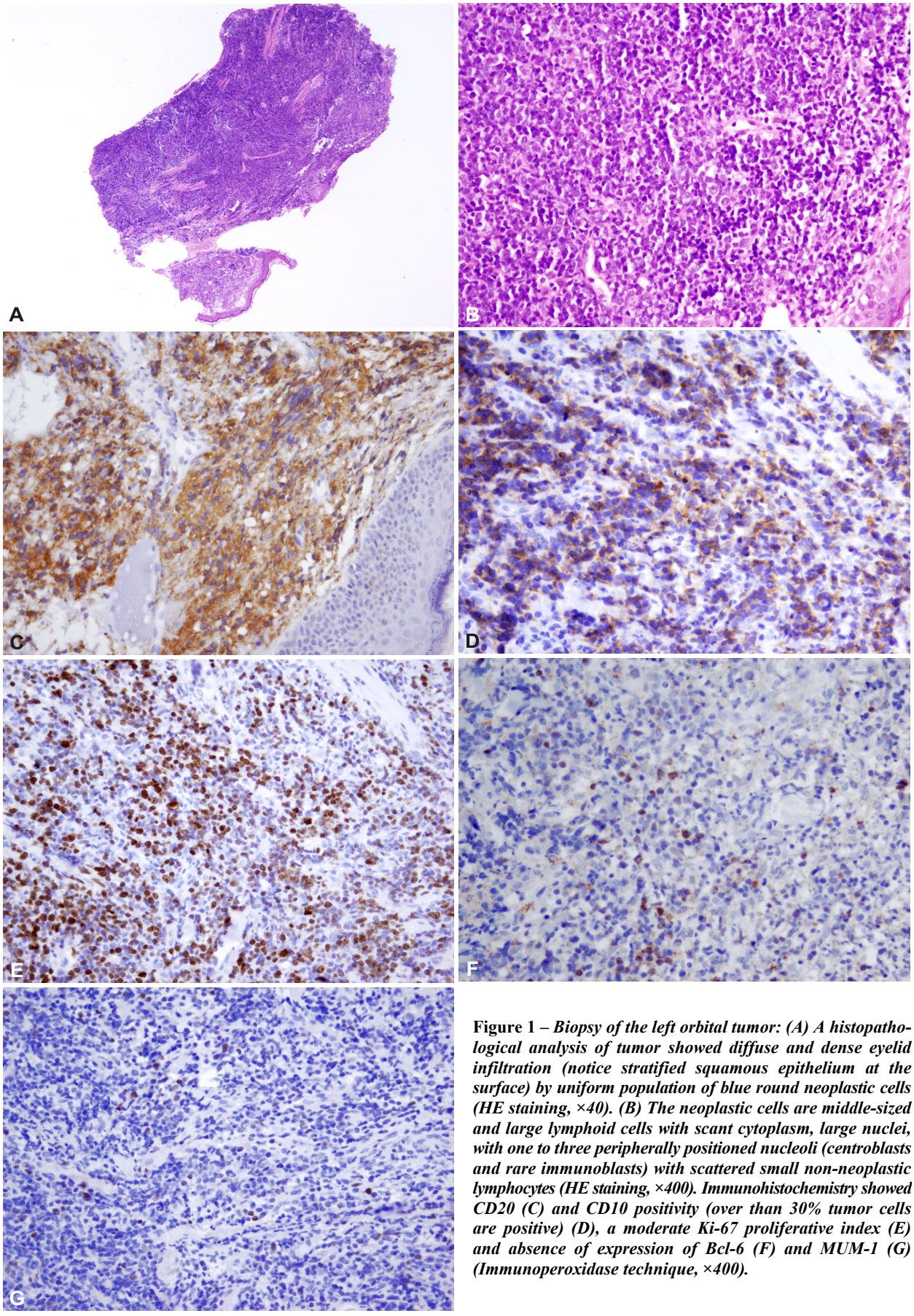

Figure 1 – ***Biopsy of the left orbital tumor: (A) A histopathological analysis of tumor showed diffuse and dense eyelid infiltration (notice stratified squamous epithelium at the surface) by uniform population of blue round neoplastic cells (HE staining, ×40). (B) The neoplastic cells are middle-sized and large lymphoid cells with scant cytoplasm, large nuclei, with one to three peripherally positioned nucleoli (centroblasts and rare immunoblasts) with scattered small non-neoplastic lymphocytes (HE staining, ×400). Immunohistochemistry showed CD20 (C) and CD10 positivity (over than 30% tumor cells are positive) (D), a moderate Ki-67 proliferative index (E) and absence of expression of Bcl-6 (F) and MUM-1 (G) (Immunoperoxidase technique, ×400).***

Serum electrolyte estimation revealed discrete abnormality: serum sodium was subnormal – 129 mmol/L (137–145 mmol/L) and potassium level was slightly elevated – 5.3 mmol/L (normal range 3.6–5 mmol/L). There were no clinical suspicious of adrenal insufficiency.

Dissemination of a systemic lymphoma was excluded by chest, abdominal and pelvic computed tomography (CT) and bone marrow biopsy. Patient was staged according Ann Arbor classification as stage IEA (localized disease).

Therapy was initiated as per the De Angelis protocol for central nervous system (CNS) lymphomas. After completion of the first phase of treatment, full remission and complete regression of the both ocular lesions was achieved, without any complications.

Three weeks later, he was admitted again for the second cycle of chemotherapy, but after administration of chemotherapy, the patient developed signs of gastrointestinal hemorrhage and died two months after the diagnosis. Autopsy findings exclude lymphoma involvement of any organ except histopathological infiltration of cortex of both adrenal glands without evidence of a mass lesion. Morphological (Figure 2, A–C) and immunohistochemical finding of CD20 (Figure 2D) and CD10 positivity (Figure 2E) in both adrenal glands confirmed partial infiltration by the same tumor (DLBCL) like in previously diagnosed orbital localization. This occult bilateral adrenal involvement did not destruct more than 60% of the gland tissue.

Postmortem histopathological examination of both orbits showed no rest of lymphoma. With the autopsy findings, we conclude that the cause of death was massive gastrointestinal hemorrhage due to acute stomach ulcers (N^{o} VII).

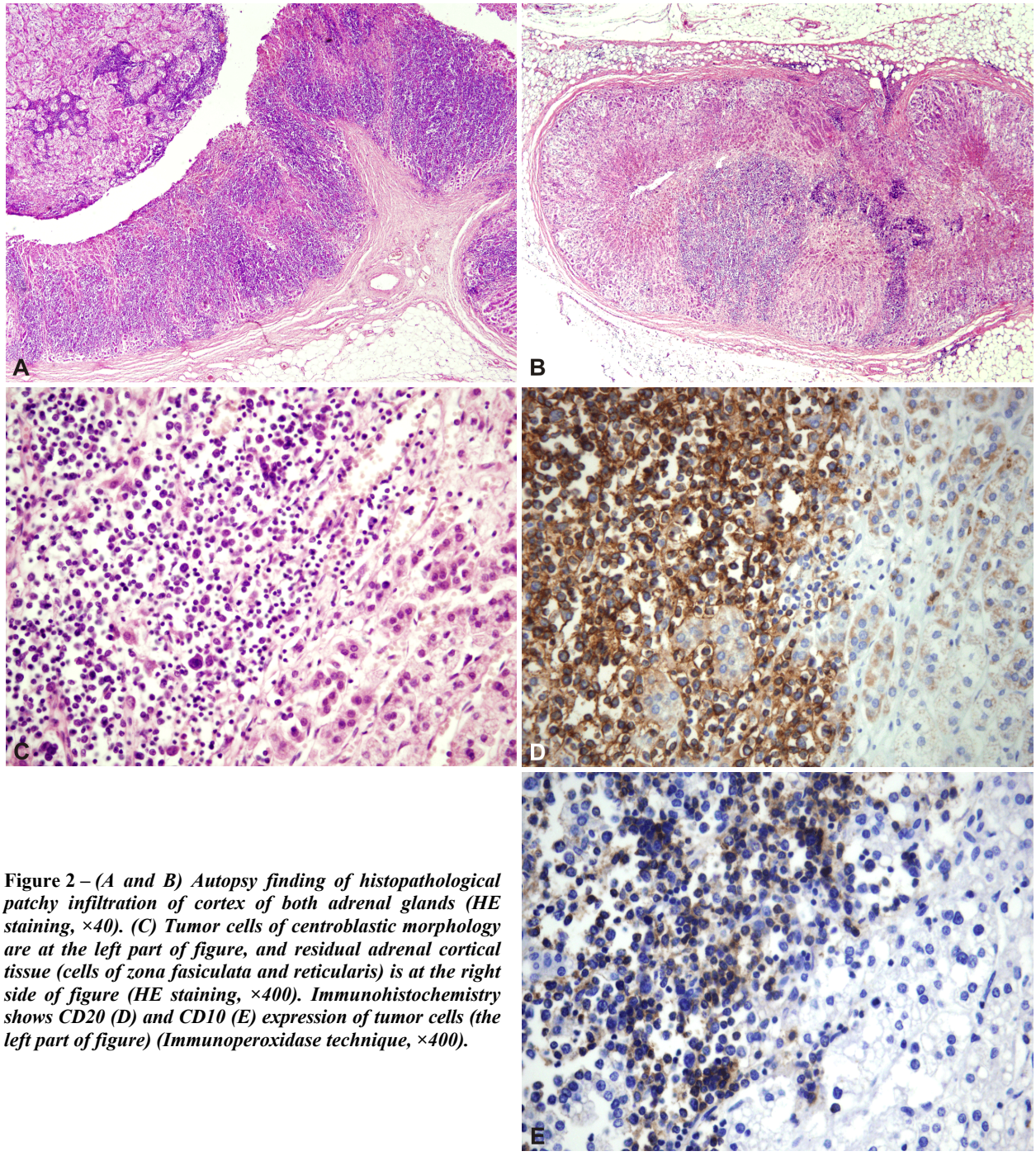

Figure 2 – ***(A and B) Autopsy finding of histopathological patchy infiltration of cortex of both adrenal glands (HE staining, ×40). (C) Tumor cells of centroblastic morphology are at the left part of figure, and residual adrenal cortical tissue (cells of zona fasiculata and reticularis) is at the right side of figure (HE staining, ×400). Immunohistochemistry shows CD20 (D) and CD10 (E) expression of tumor cells (the left part of figure) (Immunoperoxidase technique, ×400).***

Discussion

Our case has several notable characteristics. First, OL is a rare malignancy, constituting 1% of all non-Hodgkin's lymphomas (NHL) [1] and 5–14% of all extra-nodal lymphomas [2]. Of patients with bilateral orbital lymphoma, 46% had presence of systemic lymphoma at diagnosis compared to 14% where tumor was unilateral [3]. According to the same author, prior, concurrent and future extra-orbital spread was significantly associated with bilateral orbital lymphoma [hazard ratio (HR) 2.9, 95% confidence interval (CI) 1.1–2.2] [3]. However, none of 326 patients with orbital lymphoma in study of Jenkins *et al.* had involvement of adrenal glands [3]. Isolated bilateral adrenal involvement is extremely rare in OL, described in 0.83% of cases [4].

Also, adrenal lymphoma can be discovered as incidentaloma when imaging investigation for non-adrenal disorder is performed. Ultrasound, CT and MRI are useful tools for detection of adrenal mass. Prevalence of adrenal incidentaloma fluctuates between 1% and 5% [5] and in that case it is usually unilateral (only 15% are bilateral) [6]. Furthermore, adrenal involvement usually occurs in widespread NHL – in 4% of cases assessed by CT [7] and in 24% at postmortem examination [8]. In the study of Paling *et al.*, adrenal masses were demonstrated only in seven patients of 173 patients with diagnosis of NHL, coincidentally with masses elsewhere [7]. Of these, five cases were diffuse large B-cell lymphoma and three patients had adrenal masses at the time of initial presentation, whereas in four cases the adrenal gland was a site of tumor recurrence after therapy. The majority of secondary adrenal lymphoma has been documented to arise in the retroperitoneal lymph node or the ipsilateral kidney [9].

Abdominal imaging investigation for staging purpose in our patient did not discover any lesions of adrenal glands. In our case the possible explanation is that solely bilateral adrenal lymphomatous infiltration was incipient (maybe present concurrent with OL) and the first occult manifestation of the systemic spread after one cycle of chemoradiotherapy (tumor recurrence or residual disease?), but it is unclear why it failed to respond to therapy that proved to be effective for primary orbital lymphoma.

Finally, adrenal insufficiency is described in two-thirds (68.5%) of the patients with bilateral adrenal lymphomatous involvement [4, 10]. It is almost equally distributed in patients with bilateral (63.13%) and unilateral (76.19%) adrenal involvement [4]. The destruction of about 90% of the gland tissue is required for the adrenal insufficiency to manifest clinically [4]. Also, in the clinically unilateral cases the microscopic involvement of the other gland (as seen in autopsy series) explains development of adrenal insufficiency [4]. Our patient had clinically silent bilateral adrenal involvement, with very discrete electrolyte imbalance, which is unusual and can be explained by partial (less than 60%) infiltration f the gland tissue because of the fatal outcome only two months after diagnosis.

Conclusions

We have experienced a very rare case of bilateral orbital lymphoma with postmortem detection of isolated occult bilateral adrenal lymphoma. A high degree of suspicion of adrenal involvement is important to obtain a diagnosis quickly and initiate treatment since prognosis of adrenal lymphoma is poor. Extra-orbital lymphomatous infiltration significantly alters the choice of treatment for orbital lymphoma.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

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