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Very late relapse of Burkitt's lymphoma in an EBV-negative patient after 20 years of complete remission

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ABSTRACT

Burkitt's lymphoma (BL) is an aggressive B-cell lymphoma that occurs in children and adults. It is a chemosensitive lymphoma with very exceptional cases of late relapse.

We report the case of a 32-year-old male, originally from a nonendemic area for BL, who was successfully treated for abdominal BL 20 years ago. He described a two-month history of cervical swelling and a one-week history of dyspnea. Physical examination was unremarkable except for a left submandibular mass that extended to the collarbone. An ultrasound of the neck revealed cervical lymphadenopathy. The patient was submitted to a lymph node biopsy with an immunohistochemical analysis, which concluded to the diagnosis of BL. Screening for recent Epstein-Barr-Virus (EBV) infection was negative. We considered this a very late relapse (VLR) of the original disease, and the patient was treated according to the same initial protocol. Unfortunately, he suffered a second relapse and died.

We report an unusual case of a VLR of nonendemic BL in an EBV-negative patient, occurring 20 years after achieving complete remission following the initial chemotherapy.

1. Introduction

Burkitt's lymphoma (BL) is a highly aggressive B-cell malignant lymphoma, accounting for less than 5 % of non-Hodgkin lymphoma cases in adults [1].

Although its evolution is rapid, it is potentially curable with chemotherapy. Typically, relapse occurs within a short period of remission (less than 1 year) [2,3].

In this report, we present a case that, to the best of our knowledge, represents the longest period of complete remission followed by relapse, spanning 20 years.

2. Case report

The patient is a 32-year-old, HIV-negative man who presented to the emergency department with a chief complaint of swelling gradually increasing in size in the left submandibular region over the past two months.

His past medical history revealed a diagnosis of abdominal BL 20 years ago, for which he was diagnosed and treated in the oncology department of another University Hospital. At that time, he presented with symptoms such as weight loss, dyspnea, pleural and peritoneal effusion, and abdominal adenopathy. The diagnosis was confirmed through cytological examination of pleural fluid, revealing medium to large-sized round cells with scanty cytoplasm and one or several nucleoli. Neither bone marrow (BM) nor central nervous system (CNS) involvement was detected. The patient had not undergone cytogenetic or molecular studies at that time. Initially classified as Murphy stage III, he underwent chemotherapy following the Lymphoma Malignancy B (LMB) 89 protocol, group B. A computed tomography (CT) scan confirmed complete remission at the end of the treatment. He was followed up at the outpatient department with bi-annual consultations for 10 years. The patient later started working and was lost to follow-up for 10 years. He got married and he had three children.

The patient remained asymptomatic 20 years post-therapy until he presented with complaints of cervical swelling and fever. He denied weight loss, anorexia, and digestive symptoms.

Physical examination showed normal vital signs and revealed a mass

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extending from beneath the left mandible to the homolateral clavicle. The patient was referred to the ENT department for nasal endoscopy, which showed no evidence of cavum involvement.

A series of radiological and hematological investigations were then conducted. Cervical computed tomography (CT) revealed a sub-angulo-mandibular adenopathy mass measuring 84 × 58 mm. The cervical mass displaced the left sternocleidomastoid muscle outward, resulting in the left jugular vein thrombosis.

Based on these findings, the patient underwent a lymph node biopsy with an immunohistochemical study. Microscopic examination revealed a diffuse effacement of lymph node structure due to lymphomatous proliferation. The lymphoid cells appeared medium-sized with reduced cytoplasm and hyperchromatic nuclei, accompanied by abundant mitotic figures. The background showed numerous tingible-body macrophages. Immunohistochemical analysis demonstrated positivity for CD20, CD19, Bcl6, C-Myc, and MUM1, with increased Ki67 expression. These findings confirmed the diagnosis of a relapse of the prior BL (Fig. 1).

The search for factors contributing to relapse included screening for recent Epstein-Barr Virus (EBV) infection, which yielded negative results. The anti-VCA profile (IgG > 400 UI/ml, IgM = 3 UI/ml) and anti-EBNA profile (IgG > 800 UI/ml) were consistent with acquired immunity, indicative of a past infection.

The myelogram revealed a BM infiltration of 59 % by BL cells, with basophilic, vacuolated cytoplasm evident on a Wright–Giesma–stained aspirate smear. The cytogenetic study revealed the presence of the t (8;14) translocation in most mitoses, along with additional structural abnormalities on chromosomes 1 and 7.

The cervical-thoracic-abdominal-pelvic (C-TAP) CT revealed a left cervical lymph node mass measuring 10.46 × 7.35 cm, along with heterogeneous enhancement adenopathy in the right sector II measuring 2.83 × 1.98 cm. No additional nodal or extranodal lesions were detected. The cerebrospinal fluid examination was normal.

Based on these findings, the patient received treatment according to the protocol for adult BL, LMB 02 group C1.

He received six cycles of chemotherapy (COP + COPADM no. 1 + COPADM no. 2 + CYVE no. 1 + CYVE no. 2 + first cycle of maintenance treatment (m1)). We considered adding Rituximab to the regimen, but it was not available.

A mid-treatment response evaluation was conducted, revealing a

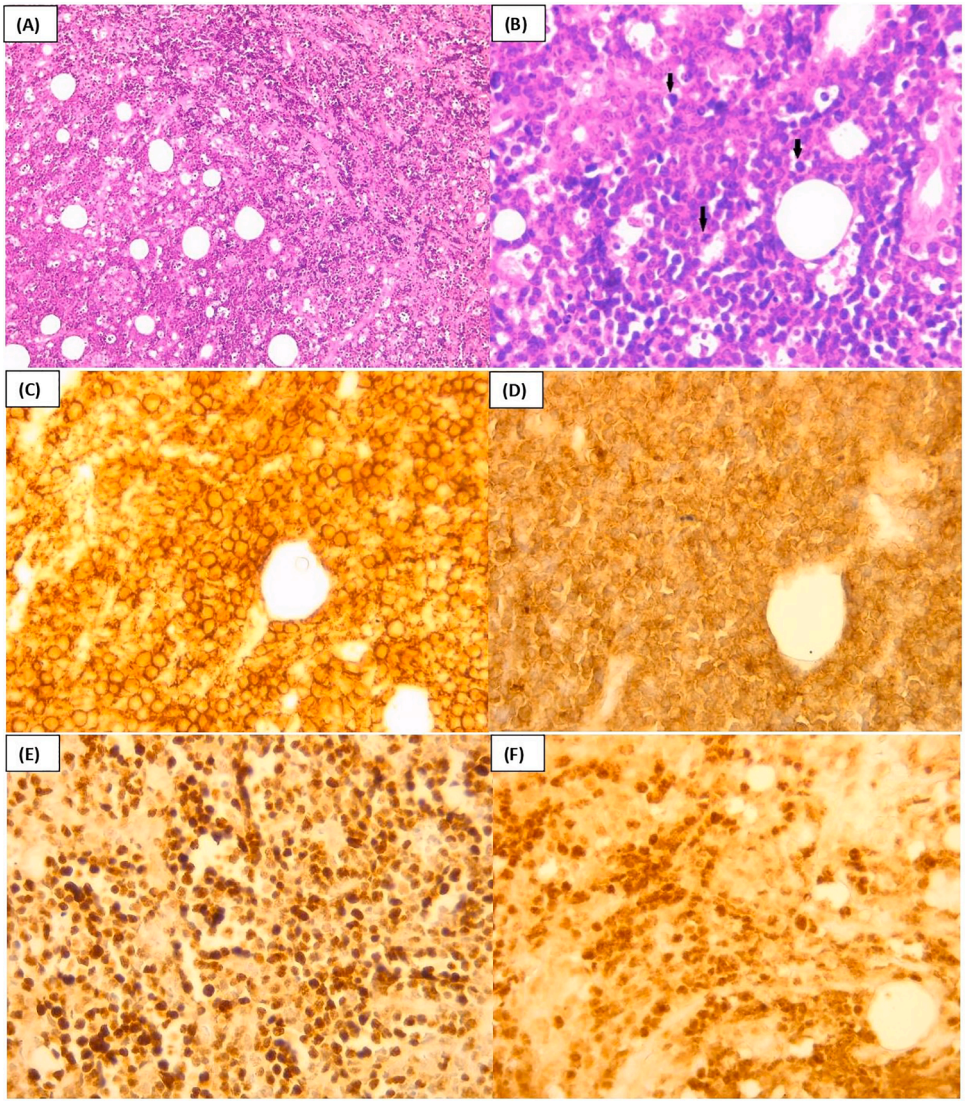

Fig. 1. Histological features of Burkitt's lymphoma: **(A) and (B):** Sheets of monotonous intermediate-size cells showing numerous mitotic figures (black arrow) and apoptotic bodies with starry sky appearance. (**A)** Hematoxylin and Eosin stain, 100x magnification, **(B)** Hematoxylin and Eosin stain, 400x magnification). **(C)** CD20 is strongly and diffusely positive (400x magnification). **(D)** CD10 is strongly and diffusely positive (400x magnification)**. (E)** Tumor cells stain positive for Bcl6 (400x magnification)**. (F)** Tumor cells stain positive for C-Myc (400x magnification).

partial clinical reduction in the mass from the sixth day of chemotherapy and its complete disappearance after the sixth cycle of chemotherapy.

The CT scan after COP demonstrated a 39 % response rate. Following CYVE no. 1, an 86 % response rate was observed, and after m1, an 89 % response rate was achieved, indicating a complete response (Fig. 2).

A subsequent myelogram conducted after COPADM no. 1 showed no medullary involvement.

Unfortunately, a second early lymph node relapse was observed one month after m1. Salvage treatment was initiated, and he received three cycles of chemotherapy (COP + COPADM no. 1 + COPADM no. 2). However, he passed away about three months after the second relapse of his BL.

3. Discussion

In this report, we present the case of a patient with BL who experienced a relapse 20 years after initial remission. To the best of our knowledge, this case represents the longest period of remission interval observed in patients with BL before relapse.

BL is known to be potentially curable with chemotherapy, resulting in long-term relapse-free remissions [4]. Unfortunately, a proportion of patients who initially achieve complete remission experience relapse. Most relapses are observed within the first year of complete remission. Two types of relapse are described in BL: early relapses occurring within 3 months of initial treatment, and late relapses occurring after more than 3 months of remission. Very late relapse refers to a recurrence more than 3 years after the diagnosis [1,5].

Late relapses of BL are quite unusual in non-endemic areas and are typically associated with EBV-positive cases [5]. Since EBV serology was negative in our patient, this makes our case particularly exceptional.

Additionally, the risk of very late relapse (VLR) rises with the occurrence of meningeal disease and/or early relapses. The use of intrathecal methotrexate significantly reduces the risk of VLRs in BL [6]. Our patient was initially treated with the LMB 89 protocol group B [2] and received intrathecal methotrexate as prophylaxis. Despite this, he experienced a relapse, making our case noteworthy.

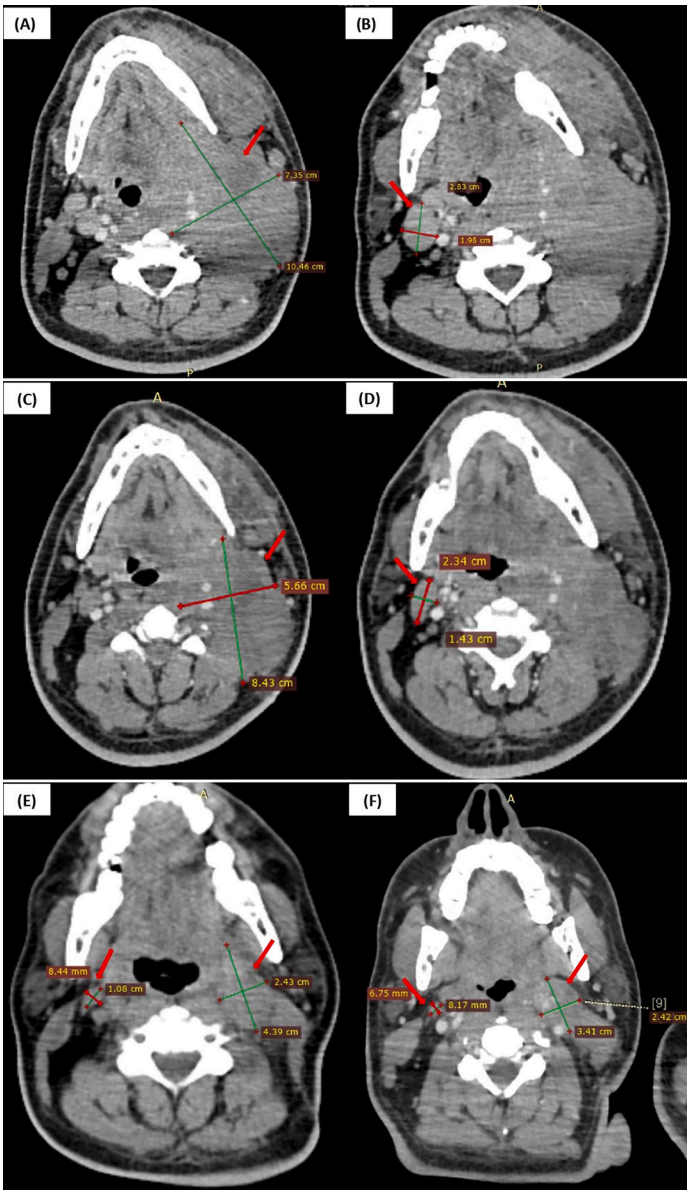

Fig. 2. Evaluation of treatment response on CT scans: **(A)** Initial left cervical lymph node mass. **(B)** Initial right cervical lymph node mass. **(C)** Post-COP CT scan showing a reduction in left cervical lymph node mass size. **(D)** Post-COP CT scan showing a reduction in right cervical lymph node mass size. **(E)** Post-CYVE no. 1 CT scan showing 86 % response rate. **(F)** CT scan post first cycle of maintenance treatment showing 89 % response rate, indicating complete response.

Late or VLRs are often attributed to the emergence of a new malignant clone rather than a recurrence of the initially treated lymphoma. The study of Ig gene rearrangement in both the initial and recurrent diseases can help determine whether they originate from the same clone or different clonal origins [1,7]. Unfortunately, the identification of Ig gene rearrangements between initial and recurrent disease was not available in our case.

John Lister et al. reported the case of a 28-year-old man who was treated for two occurrences of BL, 15 years apart. It was the first publication to demonstrate that the two BLs are clonally distinct by PCR clonality analysis. The patient was treated with chemotherapy (CHOP-M: cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate) and intra-thecal chemotherapy treatments with complete remission. He subsequently benefited from autologous stem cell transplantation with continuous complete remission after transplantation [7].

Italiano et al. reported a case of sustained remission in an adult with a relapsed disease after 17 years treated by dose-intensive chemotherapy plus rituximab. The patient had an abdominal presentation of his BL both at the initial diagnosis and at the time of relapse. The study of Ig gene rearrangement in both primary and second lymphoma was not performed in this case. The patient was treated according to the LMB 84 protocol with the addition at the relapse of Rituximab (375 mg/m^2, 6 cycles) at the first day of each chemotherapy regimen [1].

In our case, the identification of the clone responsible for disease recurrence was not studied, even the possibility that it might be the same one was strongly considered. Consequently, we opted to administer a treatment regimen similar to that used for the initial disease. We considered adding Rituximab to enhance therapeutic outcomes, but it was not available.

Although the first-line treatment for this type of lymphoma typically leads to positive outcomes, the prognosis for relapsed patients remains poor. In a single-center study by Short et al. of 145 patients with BL or high-grade B-cell lymphoma treated with hyper-CVAD, 35 patients with relapsed or refractory disease were reported. Only 39 % of patients responded to second-line therapy. Median OS was 2.8 months, and only two patients were alive at 48 months [8]. Our case underscores the poor prognosis associated with relapsed BL, as our patient passed away due to the progression of his relapsed disease.

The literature on late relapses of BL has investigated its causes and therapeutic options, yet few cases of VLR have been reported. In our study, we presented an unusual case of a VLR of BL, occurring 20 years after the initial remission, highlighting the importance of considering this possibility when faced with suggestive symptoms and exploring effective salvage treatments, regardless of the underlying cause.

4. Conclusion

VLR is extremely uncommon in nonendemic areas. EBV serology is frequently positive in this type of relapse, however, in our case no association with EBV was found.

In cases of late relapse of BL, the identification of Ig gene rearrangements between the initial and subsequent diseases is an intriguing way to show whether they came from the same clone or not. In our case, we didn't analyze it, but we strongly believed it was the same clone. Consequently, our observation represents, to the best of our knowledge, the longest period of complete remission followed by a relapse reported to date, occurring in an EBV-negative patient, 20 years after achieving complete remission from the initial chemotherapy.

Informed consent

Informed consent from the patient and authorization for publishing the case were obtained.

CRediT authorship contribution statement

Kmar Mrad: Writing – original draft. **Nader Slama:** Writing – original draft. **Nouha Ben Abdeljalil:** Supervision. **Zaineb Mlayah:** Writing – original draft. **Wiem Boufrikha:** Writing – original draft. **Abdelfattah Zakhama:** Supervision. **Sarra Boukhris:** Supervision. **Mohamed Adnene Laatiri:** Supervision.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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