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Case Report

Therapy related complications in plasmablastic lymphoma in immunocompetent individual

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Abstract: Background: Plasmablastic lymphoma (PBL) is a rare and aggressive subtype of diffuse large B-cell lymphoma seen in immunocompromised individuals. It has a diffuse growth pattern, with no standard therapy and a poor survival rate. Due to overlap in presenting features with lymphoma and myeloma, PBL is often a diagnostic dilemma. We present a case of PBL in a young immunocompetent female who developed treatment associated complications. Case report: A 36-year-old presented with a lesion extending from the oral cavity to the pharynx and involving the angle of the mandible. Radiology and laryngoscopy described a growth pattern that was diagnosed to be PBL on histopathology. The patient underwent chemotherapy using level II DA-EPOCH (dose-adjusted-etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) and prophylactic granulocyte-colony stimulating factor along with radiotherapy and ultimately, achieved metabolic response. However, she developed several episodes of paralytic ileus, cytopenia, oral ulcers, dermatitis and long-standing hypothyroidism as therapy-related complications and has been on treatment for the same ever since. Conclusions: Thus, a high index of suspicion is necessary for early diagnosis and rapid initiation of therapy. Further, there is a need to detect and address therapy related complications early to prevent long-standing, therapy-related side effects from developing and deteriorating the patient's quality of life.

Keywords: Plasmablastic lymphoma, oral cavity, immunocompetent, therapy related complications

Introduction

Plasmablastic lymphoma (PBL) was identified in 1997 by Delecluse and colleagues in HIV-positive individuals [1]. It is a rare, aggressive subtype of non-Hodgkin's lymphoma that has now been categorized as a subtype of diffuse large B-cell lymphoma, which is predominantly seen in immunocompromised patients, especially with HIV or EBV infection, and has also been diagnosed in immunosuppressed individuals in conditions such as post-transplant procedures, autoimmune diseases, and old age [2]. Few cases have, however, also been diagnosed in immunocompetent individuals [3]. It is predisposed to affect the oral cavity followed by gastrointestinal tract. Most PBLs present with asymptomatic oral swellings, without B symptoms suggesting exclusive local involvement [4]. The disease is also known to present with symptoms mimicking those of myeloma, lymphoma and even reactive periodontal conditions [5, 6]. The median age of developing PBL is 58.41 years in HIV-negative cases with a predilection towards males [7, 8]. A diagnosis of PBL is based on histopathological finding of monomorphic sheets of intermediate to large cells with plasmablastic or immunoblastic features along with correlation with clinical features, radiological findings and serum protein electrophoresis (SPEP) to rule out plasma cell myeloma [9]. Currently, treatment modalities using EPOCH (etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide and doxorubicin hydrochloride) have shown to improve survival [10]. However, prognosis remains unfavorable along with development of complications such as cytopenia associated with therapy-related toxicity [11]. Here, we report a young immunocompetent female suffering from PBL who developed treatment-related complications despite timely treatment.

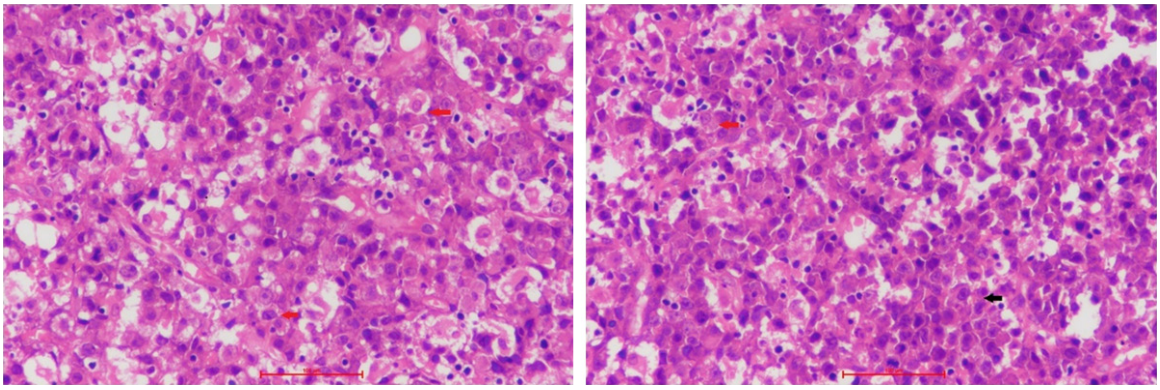

Figure 1. H&E section of biopsy from base of tongue showing sheets of atypical lymphoid cells (←) admixed with plasmacytoid and mature plasma cells (←). Atypical cells are intermediate to large sized with round eccentric nuclei, prominent nucleoli and moderate amount of cytoplasm. Increased mitotic figures and apoptotic bodies present. No necrosis or angio-destruction could be seen (400×).

Case presentation

A 36-year-old female presented with a right-sided swelling over the angle of mandible that was associated with difficulty in mouth-opening and dysphagia. Fiber optic laryngoscopy demonstrated a large growth on the right side of the base of the tongue, extending to the adjacent pharyngeal lateral wall. The patient also exhibited grade II tonsil enlargement. Radiological examination revealed a right supraglottic soft tissue lesion involving bilateral epiglottis and epiglottic vallecula along with enlarged right cervical lymph nodes. Positron emission tomography-computed tomography (PET-CT) also indicated that the lesion was metabolically active. Fine needle aspiration cytology suggested an inflammatory lesion.

On histopathological examination, however, biopsy showed atypical lymphoid cells present in sheets admixed with plasmacytoid and mature plasma cells with no signs of necrosis and angio-destruction (**Figure 1**). Immunophenotyping showed that the cells were positive for CD43, CD138, CD38, EMA, CD45RO. They were negative for CD20, CD79a, CD3, CD7a, CD5, CD30, Bcl2, Bcl6, CD23, CD10, pan-cytokeratin and weakly positive for PAX5. Kappa (κ) light chains were present in a more significant amount than the lambda (λ) light chains. Ki67 proliferation index was estimated to be 30%. Bone marrow biopsy did not show any lymphomatous infiltrate. The panel for viral markers also came out negative. MIB index was 70-80% and SPEP was negative. Serum lactate dehydrogenase, calcium and albumin levels and complete blood count were within the normal range. Positron emission tomography-computed tomography (PET-CT) also revealed a lesion at the base of the tongue extending bilaterally to the cervical lymph nodes. The disease was aggressive in nature and non-Hodgkin's lymphoma Lugano stage II E was suggested.

The patient received 6 cycles of level II DA-EPOCH (dose-adjusted-etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) for 6 months with vincristine capping. She showed no adverse effects to chemotherapy except an episode of vincristine-induced paralytic ileus, which was managed conservatively. After the second cycle, granulocyte-colony stimulating factor (G-CSF) was administered prophylactically against cytopenia. However, despite this, in the following cycle, she developed both vincristine-induced paralytic ileus and neutropenia. Her neutrophil count returned to normal levels within 15 days. High-dose contrast-enhanced CT (CECT) performed subsequently revealed the presence of progressive disease. After the fourth cycle, the patient seemed clinically better with no palpable nodes and PET-CT showed a metabolic response. Following the subsequent cycle, she showed grade III thrombocytopenia and febrile neutropenia, which was managed conservatively. The patient was also administered intrathecal methotrexate. Infrared radiotherapy was then provided to the patient at 36 Gy/20 cycles to the Waldeyer's ring and the neck region bilaterally. After this, she was clinically asymptomatic

except for radiation-induced dermatitis and oral ulceration. They were treated accordingly. The subsequent PET-CT did not show any active lesion consistent with complete remission. However, she developed radiation-induced hypothyroidism, which is currently under treatment. The patient is alive and well and has been on regular follow-up for the past 2 years and 7 months.

Discussion

PBL is a rare, aggressive subtype of non-Hodgkin's lymphoma commonly associated with HIV- and EBV-infected individuals. It originates from plasmablasts during B-cell maturation into plasma cells. After activation, B cells move to the germinal center where they move across the light and dark zone in a process called affinity maturation. B cells undergo immunoglobulin class switching and somatic hypermutation during the process to generate high-affinity antibodies to a specific antigen. B cells differentiate into plasmablasts which mature into plasma cells in the germinal center. It has been suggested that mutations in MYC oncogene in plasmablasts result in PBL. MYC is involved in cell growth, proliferation and survival and is expressed in B-cells of the germinal center. MYC rearrangements usually involve light chain immunoglobulin κ and λ, similar to the increase in κ chain levels in our patient [3]. This dysregulation is due to the presence of translocation leading to loss of cell cycle control and eventually, lymphoma [12].

PBL mostly presents in the oral cavity as asymptomatic swellings and the patients do not exhibit any B symptoms, which was seen in our patient as well. It is often misdiagnosed as infectious diseases and other malignancies such as squamous cell carcinoma as they frequently present as oral lesions as well [4].

PBL exhibits a diffuse growth pattern with large plasma cells that lack B-cell markers, i.e., CD20 and PAX5, and express CD38, CD138, MUM1, Blimp1, XBP1, and MYC [13]. These cells also have a variable expression of CD79a, EMA, and CD30 [9]. These findings are consistent with the presentation and immunophenotyping of our own case.

Treatment options involve various chemotherapeutic regimens-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), DA-EPOCH, Hyper CVAD-MA (Hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, and high dose methotrexate and cytarabine), CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high dose methotrexate/ifosfamide, etoposide, and high dose cytarabine) and COMB (cyclophosphamide, oncovin, methyl-CCNU, and bleomycin) [10, 14]. Radiotherapy is employed in localized regions in refractory settings. The treatment outcome in both immunocompromised and immunocompetent patients is poor [11]. Thus, there is no standard therapy recommended in cases of PBL and the median survival time for HIV-negative patients is 6-19 months [8]. Patients undergoing therapy often end up suffering from complications including cytopenia, neutropenic fever, immunosuppression and chemotherapy-related toxicities such as gastrointestinal (GI) side effects and hair loss [11]. Radiation therapy has more permanent and widespread side-effects ranging from fatigue, hair loss, loss of memory, hypo-functioning endocrine glands and often infertility [15].

Our patient underwent a standard DA-EPOCH chemotherapy as per current accepted protocols. However, she still developed GI side effects such as vincristine-induced paralytic ileus. In spite of its conservative management and the prophylactic steps taken to counter possible cytopenia, the patient developed both paralytic ileus and neutropenia with additional thrombocytopenia in the subsequent cycles. These had to be managed specifically at each cycle of treatment. The following cycles of radiotherapy, only further added to the list.

Thus, despite timely diagnosis, our patient ended up suffering from dermatitis, oral ulcers and hypothyroidism, for which she had to undergo separate and possibly long-term treatment.

Owing to the rarity of the disease, we could discuss only a single case of PBL in this report. However, due to its frequent misdiagnosis and resulting treatment failure there is a need for more extensive studies on PBL to understand its biological evolution as well as effective treatment. Further research is also required into common therapy-related adverse effects and their possible prophylaxis.

Conclusion

Our patient was treated with DA-EPOCH followed by radiotherapy, which resulted in complete remission with survival for over two years with continued follow up. However, she developed radiation-induced hypothyroidism, dermatitis and oral ulcers along with several episodes of cytopenia and paralytic ileus during the course of chemotherapy, which indicate a requirement for better treatment modalities with fewer side effects. Thus, though PBL remains a diagnostic and therapeutic dilemma that needs to be picked up early, it also requires constant vigilance to pick up on adverse effects of therapeutic modalities that may end up affecting the patient's quality of life.

Disclosure of conflict of interest

None.

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