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Case report

VERY LATE RELAPSE IN HODGKIN DISEASE: OUTCOME OF PATIENT RELAPSING MORE THAN 24 YEARS AFTER PRIMARY CHEMO- AND RADIOTHERAPY ON RARE LOCATION

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Abstract

Late Hodgkin disease refers to a recurrence of the disease after a period of remission (absence of disease symptoms). It can occur as a *de novo* (new) malignant neoplasma or as a relapse of the old disease. In some cases, late Hodgkin disease may be a new disorder that is not related to the original disease. This can occur if the patient was not properly treated for the original disease, or if the patient's immune system was compromised and developed something new. In other cases, late Hodgkin disease may be a relapse of the original disease. This means that the disease has come back after a period of remission.

We present a case of a 27-year-old male with HD after 24 years of period of complete remission of the initial disease. This very rare relapse of HD was presented on gingivae like an extranodal involvement which is less commonly found than in other lymphomas. The histopathological analysis of the gingivae during the relapse showed presence of another subtype of Hodgkin disease - nodular lymphocyte predominant (NLPHL) on a rare location.

It is important for patients to follow their treatment plan closely and to continue to see their healthcare provider for follow-up care after treatment. Our case illustrates that Hodgkin lymphoma can also appear in soft tissue masses such as gingivae and is more refractory to the standard therapeutical approach.

Keywords: Hodgkin lymphoma, late relapse, risk factors, ABVD regimen

Introduction

Hodgkin lymphoma (HL) is one of the most common cancers in young adults, where the highest incidence rates are bimodal at the age of 15-35 and over 50-55 years. HL can be classified into five different subtypes with different morphology[1]. The classic HL (cHL) is classified into four groups: nodular sclerosis (NS), mixed cellularity (MC), lymphocyte-rich (LR), and lymphocyte depletion (LD). In 1994, the revised European-American classification (REAL) recognized another subtype - nodular lymphocyte predominant (NLPHL) as a non-

classic type (only 5% of all HL), with different clinical, histological features and indolent behavior. It occurs generally at 30-40 years of age, predominantly in men, and because of its nature late relapse can develop[2-5]. The treatment of HL has improved over the past three decades. Rates for complete remission (CR) after first-line initial treatment range from 75% to over 90% depending on age, gender, histological type, stage of the disease, treatment regimen, and initial treatment outcome[1,6,7]. Considering the whole age spectrum of HL patients, approximately 20-30% will experience relapse after achieving CR, even after accurate disease staging and optimal treatment strategies. Late relapse (LR) of HL, occurring 5 or more years after the first diagnosis, is rare but real event. The incidence of LR of HL is between 2.8% and 5.6%. Very LR occasionally occurs, and there is no confirmed risk factor, but NLPHL subtype, mixed cellularity subtype, age > 45 years, male gender, ESR<50 mm, and omission of radiotherapy alone, seem to be also risk factors[8]. In particular, extranodal Hodgkin lymphoma involving soft tissues is extremely rare, especially on locations such as gingivae, skin, breast and musculoskeletal system[9]. LR is observed more frequently after early-stage favorable HL might be due to persistent, slow-growing disease initially located outside the radiotherapy fields; risk-adapted therapies where intensity is on the edge of sufficiency; or distinct biology of either host of the tumor with no current data pointing in either direction. Basically, relapses can occur because the original treatment was not effective in eliminating the disease, or because the disease has evolved and is resistant to the original treatment. It is important to note that the risk of late Hodgkin disease is also observed in patients who have had advanced stages of the disease and/or who have received certain types of treatment[10-15].

Case report

We report a case report of a 27-year-old male with initials A.S. who contacted our Clinic in May 1998 after extracting lymphadenopathy on the neck and received a histological finding of HL mixed cellularity. The laboratory and biochemical findings were normal. After the performed staging procedures, it was confirmed that the patient had HL mixed cellularity IIA without any organ involvement below the diaphragm and bone marrow. Six cycles of ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) were administered. The neck and the left axilla were also treated with radiotherapy in a total dose of 36Gy. Complete remission was achieved and in the first 5 years, regular check-ups were made. The remission lasted for 24 years until January 2022, when the patient A.S., now aged 51, complained on tooth pain and visited his dentist. One tooth was extracted and the wound could not heal for more than 2 months (Figure 1 and Figure 2). After that, he was sent for maxillofacial surgery and a biopsy from gingivae tissue was performed, showing a very late relapse of HL with the extranodal presentation on a very rare location, the gingivae. The histopathological analysis of the gingivae during the relapse showed presence of another subtype of Hodgkin disease - nodular lymphocyte predominant (NLPHL).

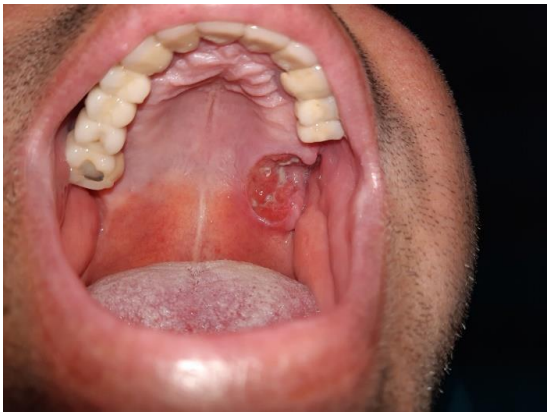

Fig. 1. Presentation of oral gingiva infiltrated with Hodgkin's disease

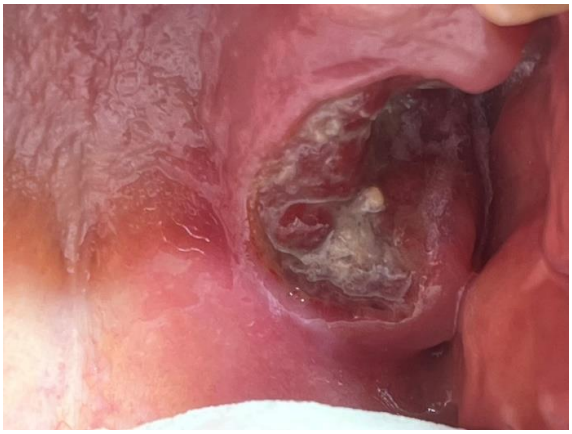

Fig. 2. Presentation of oral gingiva infiltrated with Hodgkin's disease

During the procedure, CT of the neck, thorax, and stomach was performed and confirmed soft tissue tumor and lymphadenopathy above and below the diaphragm (Figure 3 and Figure 4).

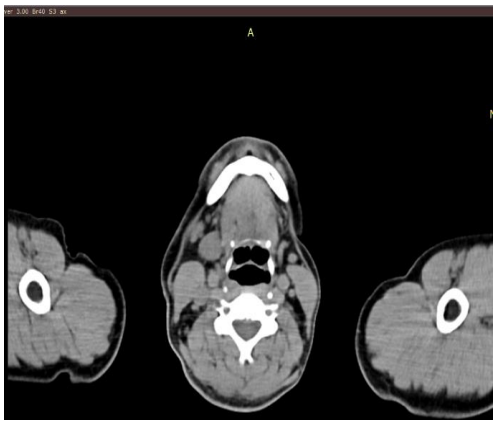

Fig. 3. CT images of the neck extranodal infiltration

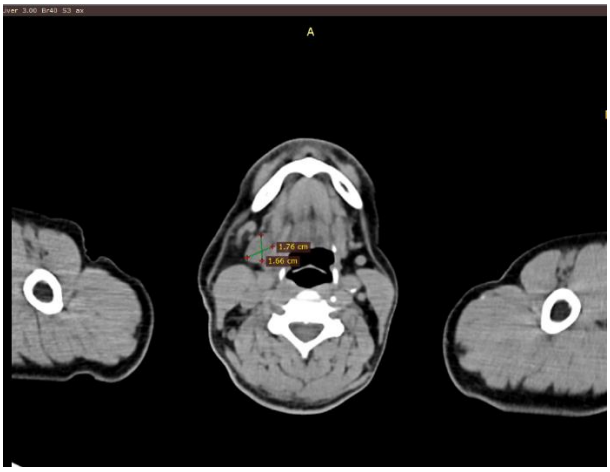

Fig. 4. CT images of the neck extranodal infiltration

Also, we performed PET scan and it showed a relapse of HL with extranodal presentation and confirmed generalized lymphadenopathy.

The patient was referred to the University Clinic for Hematology and it was decided to treat the patient as HL *de novo* again, with ABVD regimen 2 cycles and evaluation with an early interim PET scan. The second PET scan showed a progression of lymphadenopathy and affected new areas (Douville score=5), which developed during therapy application. The case was diagnosed as a very late refractory HL and it was decided to start with a high dose of DHAP regimen (Dexamethasone, high-dose Cytarabine (ARA-C), Cisplatin) and monoclonal antibodies antiCD30 Brentuximab from 2 to 4 cycles. Complete remission was achieved after 2 cycles (confirmed with a PET scan) and the treatment continued with autologous stem cell transplantation. The mobilization of the stem cells was performed with granulocyte colony-stimulating factor (GCSF) for 5 consecutive days. White blood cells (WBC)=$152x10^9$/L=$6.2x10^8$/kg precisely mononuclear cells 93%=$5.8x10^9$/kg have been harvested. The conditioning regimen BEAM (Carmustine, Etoposide, Cytarabine, Melphalan) before the procedure was administered. The autologous transplantation was achieved, with engraftment for WBC and platelets on the 13^{th} day. The patient is feeling good and now he is at home, recovering with antibacterial, antiviral, and antifungal prophylaxis in the next three months. On the regular three months follow-up, the control PET scan showed a complete remission of HD.

Discussion

The question of whether very late relapses represent a second primary disease in patients with a genetic predisposition to HL rather than a relapse of the original disease remains the subject of discussion. Can we refer to such cases with quite a long relapse period as a continuation of the old disease or a new disease with new clinical characteristics as well as outcomes?

The dilemma which arises shows that we should follow up patients for a longer period of time, and never forget that the relapse is always much more aggressive and it affects different areas of presentation compared to the initial disease. Probably the very late relapses occur in patients with the indolent nature of the disease. Although these relapses are very rare, we should still follow up patients for a longer period or maybe a lifetime?

Also, can whether if these patients with favorable characteristic HD live as long as the rest of the population? When relapse occurs in these patients, is it necessary to start initially with more aggressive treatment with monoclonal antibody plus high-dose therapy, followed by transplantation or to proceed with the initial treatment and therapy as we primarily applied

in the beginning? With adequate treatment, the prognosis of late relapse of Hodgkin disease seems favorable compared to early relapses.

Conflict of interest statement. None declared.

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