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Case Report

Rapid development of HPV-mediated oropharyngeal squamous cell carcinoma in the setting of immune suppression following autologous stem cell transplantation for Hodgkin lymphoma☆

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ABSTRACT

The patient is a 61-year-old male with a diagnosis of relapse classical Hodgkin lymphoma, treated with ABVD, ICE, and achieved remission. He underwent autologous stem cell transplantation and 3 months later found to have a PET-positive neck node concerning for relapsed disease of Hodgkin lymphoma. Biopsy proved the lesion was HPV-associated squamous cell carcinoma and not relapse Hodgkin disease. Iatrogenic immunosuppression such as bone marrow transplantation can cause substantial increase risk for viral-associated tumors and therefore tissue biopsies are necessary to make that distinction to avoid inappropriate treatment.

1. Introduction

Secondary malignant neoplasms after bone marrow transplantation are a known long-term complication which can be caused by various mechanisms, depending on the type of transplant. In allogeneic hematopoietic cell transplantations (HCT), secondary neoplasms can be caused by immunosuppression which allows oncogenic viruses to proliferate in vulnerable cells [1–3]. For autologous HCT secondary neoplasms are less frequent and are usually secondary to the chemotherapy or radiation therapy [4,5]. The latency period for the development of a secondary malignancy after autologous transplantation is usually greater than 10 years (cumulative risk of 6% at 10 years and 15% at 15 years post-transplantation) [6]. Herein, we present an unusual patient with classical Hodgkin lymphoma who developed squamous cell carcinoma of the oral cavity three months after autologous HCT.

2. Case report

The patient is a 61-year-old male with a diagnosis of classical Hodgkin lymphoma (HL) (Fig. 1A), who presented with stage IVB disease involving lymph nodes, lung, bone, and bone marrow. He had 4 high-risk international prognostic factors including age, male sex, stage IV, and hypoalbuminemia. He was treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for 6 cycles but had progression of the disease within a month after completion of ABVD. Repeat lymph node biopsy confirmed relapsed HL. He was then given ifosfamide, carboplatin, and etoposide (ICE) × 2 cycles and went into remission. He underwent autologous HCT using yttrium 90-labeled anti-CD25 antibody in combination with high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM) regimen. A follow-up positron emission tomography-computed (PET) scan at 3 months post-HCT showed a solitary lymph node in the right neck measuring 16 × 14 mm with a standardized uptake value (SUV) of 10.4 (Fig. 1B), which was concerning for relapsed disease. No other lymphadenopathy was noted. An excisional biopsy was performed and showed squamous cell carcinoma (Fig. 1C) in a 2.2 × 1.8 × 1.5 cm lymph node that was positive for cytokeratin, p16, a surrogate marker for human papillomavirus [7] (Fig. 1C, inset), and p63 by immunohistochemical staining. This profile raised concern for an HPV-mediated oropharyngeal cancer as a second primary malignancy present. Further investigation showed an ipsilateral base of tongue lesion proven to be the primary cancer by diagnostic laryngoscopy and biopsy. Definitive surgical management included base of tongue resection by transoral robotic surgery (TORS) and also modified radical neck dissection. Pathologic evaluation showed a p16-positive squamous cell carcinoma of the base of the tongue which

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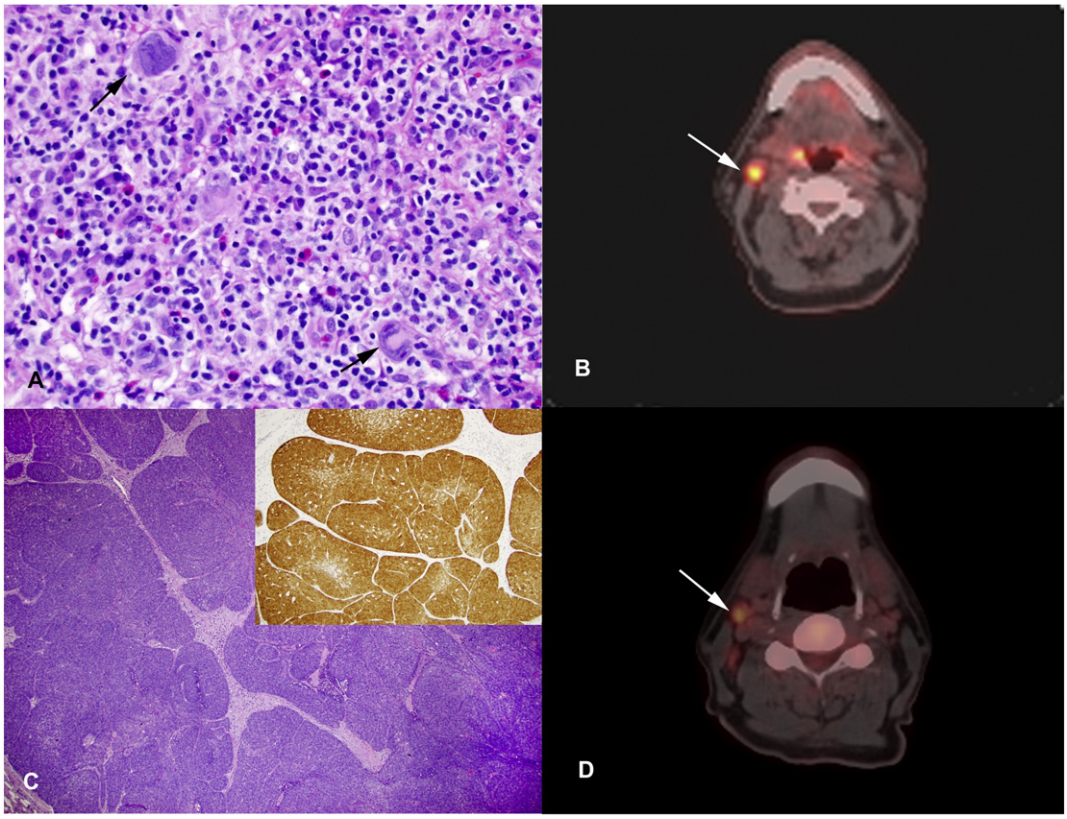

Fig. 1. A. Lymph node showing scattered Hodgkin and Reed-Sternberg cells (arrows, Hematoxylin and eosin stain). **B**. Follow-up PET scan after bone marrow transplantation shows a solitary lymph node with increased uptake (SUV 10) in the right neck. **C**. Excisional biopsy of the lymph node shows squamous cell carcinoma (Hematoxylin and eosin stain) that was also positive for p16 (inset) by immunohistochemistry. **D**. PET scan prior to transplantation showed the same solitary node but with SUV 4.7.

measured 1.9 cm with a depth of invasion of 9 mm (T1). The closest resection margin was the deep margin at 2 mm. The neck dissection yielded another involved lymph node measuring 1.0 cm and with no evidence for extracapsular extension (N2b). Final pathology stage was IVA, therefore adjuvant radiation therapy was given. A dose of 60 Gy over 30 fractions was delivered to the surgical bed in the right base of tongue and pathologically involved nodal stations in the right neck. The contralateral neck received a dose of 54 Gy over 30 fractions using dose painting IMRT technique. Patient is currently doing well 8 months following completion of the treatment and 1 year after transplant. His most recent PET/CT scan was negative.

3. Materials and methods

Formalin-fixed, paraffin-embedded tissue from the patient's sample was cut at 4 μm thickness, deparaffinized in xylene, and hydrated using serial percentages of alcohol. A hematoxylin and eosin stain was performed on the sections. Immunostains were also performed using antibodies for CD30 (clone JCM182, Leica), cytokeratin Oscar (clone Oscar, Cell Marque), PAX5 (clone 1EW, Leica), CD15 (clone MMA, BD Bioscience), p53 (clone 7JUL, Leica), and p16 (clone G175-405, Ventana). All stains were performed on the BOND immunostainer by Leica (Buffalo Grove, IL, USA) using a ready to use dilution.

4. Discussion

This case is of interest for three reasons: 1) the rapid clinical presentation of a secondary malignancy only three months after HCT, 2) the possibility that recurrent lymphadenopathy may not always be due to relapsed disease but may represent other pathology including second malignancy and 3) in an adult middle-aged male who presents with an abnormal neck node a head and neck aerodigestive primary should always be considered even in a nonsmoker. HPV-mediated oropharyngeal squamous cell carcinoma is a growing cancer demographic in this country. Today up to 70% of oropharyngeal cancer cases diagnosed in the United States are HPV mediated. Immune suppression such as that following bone marrow transplantation may increase susceptibility to HPV-mediated cancers including those that arise in the aerodigestive tract.

In summary, patients with iatrogenic immunosuppression due to organ or bone marrow transplantation are at a substantial risk for viral-associated tumors such as Epstein-Barr virus-associated lymphomas, as well as HPV-associated cancers involving the vulva, vagina, anus, and oropharynx [8–10]. This case underscores the importance of a careful physical examination, imaging review, and heightened alertness regarding synchronous malignancies inpatients being evaluated for bone marrow transplantation. HPV-mediated oropharyngeal squamous cell carcinoma (HPV-OPSCC) predominately involves the palatine and/or lingual tonsillar tissues and is not uncommon, especially in middle-aged males. HPV-OPSCC is associated with improved prognosis for overall and disease specific survival compared to tobacco mediated oropharyngeal cancers [11,12]. If this lesion had not been biopsied after the PET scan for diagnosis, the presumptive diagnosis of persistent Hodgkin lymphoma would have led to mismanagement.

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