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Original Article

A rare case of nasopharyngeal carcinoma in a patient with multiple myeloma after treatment by lenalidomide

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Abstract: Multiple myeloma (MM) is a plasma-cell malignancy leading to a significant life-expectancy shortening. Lenalidomide is an oral immunomodulatory drug (IMiD) approved in the United States for patients with MM. Although the introduction of lenalidomide combined with dexamethasone (Len/Dex) has improved the outcome of patients with relapsed/refractory multiple myeloma (RRMM), it is a common knowledge that lenalidomide has been linked to the development of secondary primary malignancies in the MM patients, especially in those who use lenalidomide as a maintenance therapy. In the published literature, these are also many cases reported by clinicians in different secondary primary malignancies after the diagnosis of MM treated with lenalidomide. In this present article, we provided our patient who was identified nasopharyngeal carcinoma (NPC) 46 months after the diagnosis of MM and 21 months after lenalidomide treatment. To the best of our knowledge, this is the first case report related to the occurrence of NPC in a patient with MM after treatment by lenalidomide. Although it is not very sure that the incidence of NPC was associated with the use of lenalidomide, we clinicians should pay adequate attention to this phenomenon in the clinical processing. And much more cooperative studies of large numbers of MM patients are needed to evaluate a possible association between lenalidomide and NPC.

Keywords: Nasopharyngeal carcinoma, multiple myeloma, lenalidomide, immunomodulatory drug

Case report

A 59-year-old man came to our hospital due to progressive back pain for nearly one month without any incentive on 3 Feb, 2009. Blood routine examination showed the WBC and PLT were normal but he was at a state of moderate anemia. The amount of hemoglobin was 77 g/L. Blood chemistry result showed globulin was at an abnormal high concentration of 74.8 g/L and albumin was at a below normal concentration of 24.3 g/L. ESR was 140 mm/H. Immunoglobulin A (IgA) was at a remarkable high concentration of 5850 mg/dl and was confirmed as a monoclonal protein by immunofixation. The concentrations of other types of immunoglobulin were below the lower normal limit. β2-microglobin was 10008 μg/L. The concentration of Kappa-Light from blood and urine was 7860 mg/dl and 58.40 mg/dl respectively. The proportion of abnormal plasma cells in bone marrow accounted for 64.5%. The cell surface of these plasma cells was CD38 positive and CD138 positive. Lumbar MRI showed: Lumbar degenerative with L3/4, L5/S1 disc degeneration, L1 vertebral wedge changes. A cytogenetic analysis showed 46, XX. Bone-ECT showed: Tracer uptake distribution on the left front rib section 2, 3, 7, 8 and 5 after the rib and right before the 5 rib, T7, T10, L1. This patient was diagnosed with multiple myeloma (MM) IgA type (Durie-Salmon stage III and International System Stage III) and he was admitted to hematology ward immediately. Subsequently, the patient underwent first cycle of PAD (Bortezomib 1.3 mg/m^2 d1, 4, 8, 11 Doxorubicin 10 mg/m^2 d1-4, Dexamethasone 40 mg d1-2, 4-5, 8-9, 11-12, every 21 days) chemotherapy from 9 Feb, 2009. The second course was postponed to 10 Apr, 2009 due to severe herpes zoster. Before the second chemotherapy, the reviewed results showed the IgA was dropped to 166 mg/dl and the immunofixation electrophoresis was negative. The patient got a complete response (CR) according to both the EBMT and

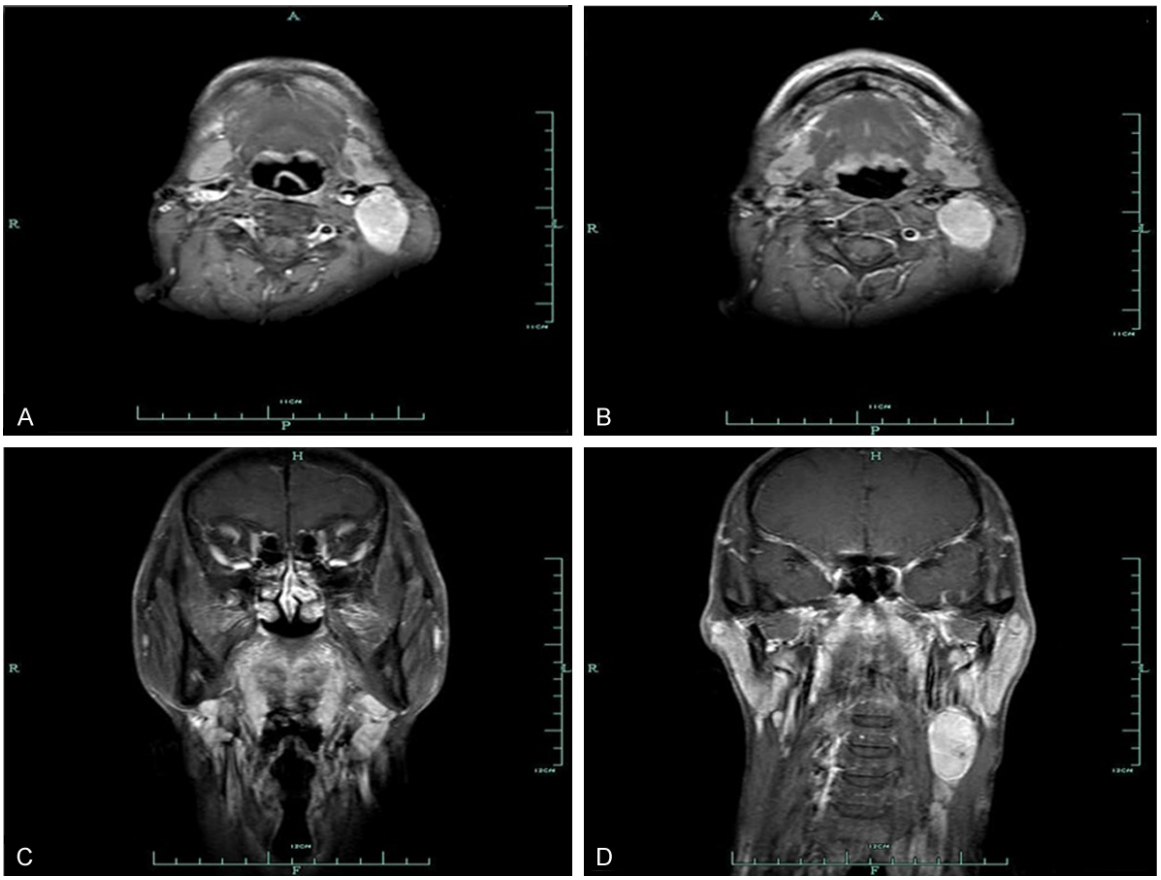

Figure 1. The sinuses MR (T1W) indicated: Top of the posterior wall of the nasopharynx mucosal was thickened, obviously in the left side and irregular soft tissue mass was in deep visible. Enlarged lymph nodes were seen on the left side of the neck and part of them integrated together.

IMWG standard. Five additional PAD chemotherapy regimens were given for consolidation in the following and the chemotherapy was stopped for this patient since 11 Aug, 2009. Unfortunately, the examination showed an increased IgA during the outpatient follow-up from 28 Jan, 2011. The patient encountered progressive disease (PD) on 15 Mar, 2011. At this point, the patient preferred Rd chemotherapy (lenalidomide 25 mg orally qd d1-21, dexamethasone 40 mg orally d1, 8, 15, 22, every 28 days). After two cycles, the patient got CR again. The Rd regimen was continued until 4 Oct, 2012 because the patient fell into asymptomatic relapse again and the patient came to the hematology clinic monthly for monitoring MM status. When the patient presented to our hospital due to nasal congestion and runny nose with bloodshot for half a month on 12 Dec, 2012, the sinuses MR indicated the two nasopharyngeal wall soft tissue were apparent hyperplasia, especially in the left side together with lymphadenopathy in the left neck (**Figure 1**). Tissue biopsy under nasopharyngoscopy confirmed it was the Nasopharyngeal Carcinoma (NPC), with the subtype of non-keratinizing differentiated carcinoma (**Figure 2**) and the EBV-DNA test was negative simultaneously. The patient was diagnosed as NPC, at a stage of T2N3M0 (according to the AJCC for NPC, seventh edition 2010). The patient was administrated concurrent radiotherapy and chemotherapy in our hospital for NPC. Radiation dose: Dt: 5450cGy/25f, 218cGy/f, 5f/W and chemotherapy regimen was cisplatin plus 5-Fu (cisplatin 40 mg d1-3, 5-Fu 5.0 g civ q96h) for 4 cycles. Due to intolerable side-effect, the treatment for NPC was stopped on 4 Apr, 2014 and the patient entered into follow-up in the outpatient for both MM and NPC. Until now, more than one year past, the patient was at stable disease for both MM and NPC.

Discussion

Multiple myeloma (MM) accounts for 1.5% of all cancers and approximately 13% of all hemato-

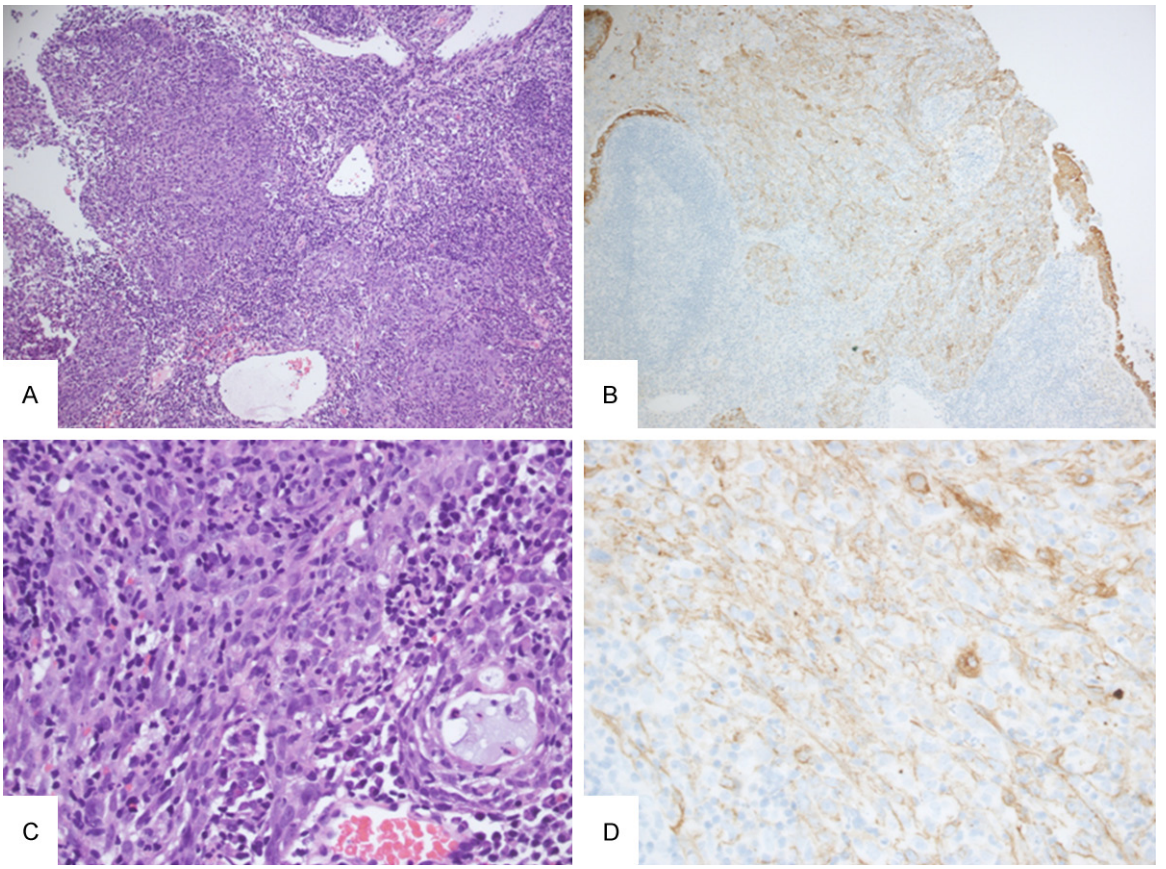

Figure 2. A-D: Immunohistochemical staining of tissue biopsy under nasopharyngoscopy was performed and there were a large number of lymphocytes and piles of atypical cells. A: Hematoxylin and eosin staining; magnification ×100; B: Immunohisto-chemical staining of CK was positive; magnification ×100; C: Hematoxylin and eosin staining; magnification ×400; D: Immunohisto-chemical staining of CK was positive; magnification ×400.

logic malignancies. Approximately 86,000 new cases of MM were reported annually worldwide [1]. Lenalidomide is an oral immunomodulatory drug (IMiD) approved in the United States for patients with MM. The introduction of lenalidomide combined with dexamethasone (Len/Dex) has improved the outcome of patients with relapsed/refractory multiple myeloma (RRMM) to a great extend [2]. However, the Food and Drug Administration (FDA) also reported an increased risk of developing ALL, AML, myelodysplastic syndromes, Hodgkin's lymphoma, and other B-cell malignancies after chronic use of lenalidomide to treat MM [3]. Although, the mechanism of lenalidomide causing secondary malignancies has not been fully elucidated, case reports and phase 3 trials have captured this uncommon occurrence [4, 5]. Among all the reports and trials, IFM trial and CALGB trial are the representatives. In both IFM and the CALGB-trial the authors pointed a concerning finding is the increase in the incidence of secondary malignancies (SMs) at a median follow-up of 1.6-3.1 years, increased approximately 2-fold in the lenalidomide maintenance arm and in particular, acute myeloid leukemia (AML)/myelodysplastic syndromes (MDS) in the MM patients who take the lenalidomide as the maintenance therapy [6-8]. Palumbo et al considered exposure to lenalidomide plus oral melphalan significantly increased hematological second primary malignancy risk versus melphalan alone. However, exposure to lenalidomide plus cyclophosphamide or lenalidomide plus dexamethasone did not increase hematological second primary malignancy risk versus melphalan alone. They concluded that patients with newly diagnosed myeloma who received lenalidomide had an increased risk of developing hematological second primary malignancies and suggested that alternatives, such as cyclophosphamide or alkylating-free combina-

tions, should be considered instead of oral melphalan in combination with lenalidomide for myeloma [9].

Herein, we would like to present our experience in a patient with MM, who developed nasopharyngeal carcinoma (NPC), 46 months after the diagnosis of MM and 21 months after the initial lenalidomide treatment. Our case study documented the unusual presentation of NPC arising in a patient with lenalidomide previously treated MM. This very rare clinical course raises several important questions, among them the relationship between MM, lenalidomide, and NPC. The association of MM, lenalidomide and NPC, the clinical setting and pathological findings described here has not previously been reported. In our case, the association between MM, therapy with lenalidomide and NPC remains unknown. Herein, we authors prefer to believe NPC as a late complication of MM as the result of lenalidomide chemotherapy.

Although, the former reports and FDA pointed out lenaidomide related to the secondary hematological malignancies are mostly confined to AML,MDS and HD [9-12], these are more and more cases reported by clinicians in different secondary primary malignancies after the diagnosis of MM treated with lenalidomide in the published literature, such as acute lymphoblastic leukemia (ALL) [13, 14]. To the best of our knowledge, there is no formal peer review publication describing the development of NPC due to chronic lenalinomide therapy. We clinicians should be kept in mind that the development of a more aggressive neoplasm related to chemotherapy treatment as well as the inherent genetic instability of normal and abnormal MM and a longer follow-up is needed to characterize second tumor risks in the IMiD era. Further studies are needed to identify risk factors for development of secondary malignancy and the best management approach for these patients.

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Disclosure of conflict of interest

None.

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