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Case Presentation

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Clinical Amyopathic Dermatomyositis Associated with Epstein–Barr Virus-Positive Large Cell Neuroendocrine Carcinoma of the Nasopharynx: A Case Report and Literature Review

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Abstract

This report describes an extremely rare case of clinical amyopathic dermatomyositis (CADM) associated with Epstein–Barr virus (EBV)-positive large cell neuroendocrine carcinoma (LCNEC) arising in the nasopharynx. An early 60s man, who presented with characteristic cutaneous manifestations of CADM, was diagnosed with a

nasopharynx tumor during screening for underlying malignancies. Biopsy of the mass revealed large cells arranged in confluent nests, with moderate amounts of basophilic cytoplasm, a relatively high cytoplasmic to nuclear ratio, and obvious large nuclei with mitotic figures. Immunohistochemical analyses confirmed the presence of neuroendocrine carcinomas, and in-situ hybridization was positive for EBV-RNA. Positron emission tomography/computed tomography revealed no metastases. To our knowledge, this is the first report of CADM associated with EBV-positive LCNEC arising in the nasopharynx. Screening for potential malignancies is important, especially in male patients in the Chinese population.

Keywords: Clinical amyopathic dermatomyositis; Large cell neuroendocrine carcinoma; Epstein–Barr virus; Nasopharynx; Case report

Nomenclature: CADM: Clinical Amyopathic Dermatomyositis; EBV: Epstein–Barr Virus; LCNEC: Large Cell Neuroendocrine Carcinoma; NEC: Neuroendocrine Carcinomas; EMA: Epithelial Membrane Antigen; FDG-PET/CT: Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography.

Introduction

Clinical Amyopathic Dermatomyositis (CADM), characterized by typical cutaneous manifestations without overt muscle involvement, belongs to a subgroup of idiopathic inflammatory myopathies [1]. The association of dermatomyositis with various types of malignancies has been well established, and dermatomyositis is hence a potentially paraneoplastic disorder [2]. Nasopharyngeal carcinoma, an Epstein–Barr Virus (EBV)-associated malignancy, has been reported to be associated with dermatomyositis [3]. Neuroendocrine Carcinomas (NEC), first described in the lungs and subsequently in many other sites, are rare in the nasopharynx [4,5]. Large Cell Neuroendocrine Carcinoma (LCNEC) is a poorly differentiated category of NEC, only documented in a few cases [5-9]. To the best of our knowledge, only four cases of EBV-positive LCNEC in the nasopharynx have been reported [6-9]. Herein, we describe the first reported case of CADM associated with EBV-positive LCNEC arising in the nasopharynx.

Case Description

A 64-year-old male was admitted with complaints of a facial and upper chest erythematous rash for the previous six months, with worsening for the prior one week. Characteristic cutaneous manifestations of CADM, including heliotrope, V-sign rash, and Gottron signs, were observed **(Figure 1),** but muscular symptoms were absent. Serum levels of creatine kinase and lactate dehydrogenase were 347 U/L and 295 U/L, respectively. Autoimmune serology demonstrated a weakly positive antinuclear antibody (1:80, cytoplasmic fine speckled) and a positive anti-Ro 52. Tests for other myositis-associated and myositis-specific autoantibodies were negative. During routine screening for underlying malignancies, nasopharyngoscopy revealed an obvious tissue mass in the roof of the nasopharynx.

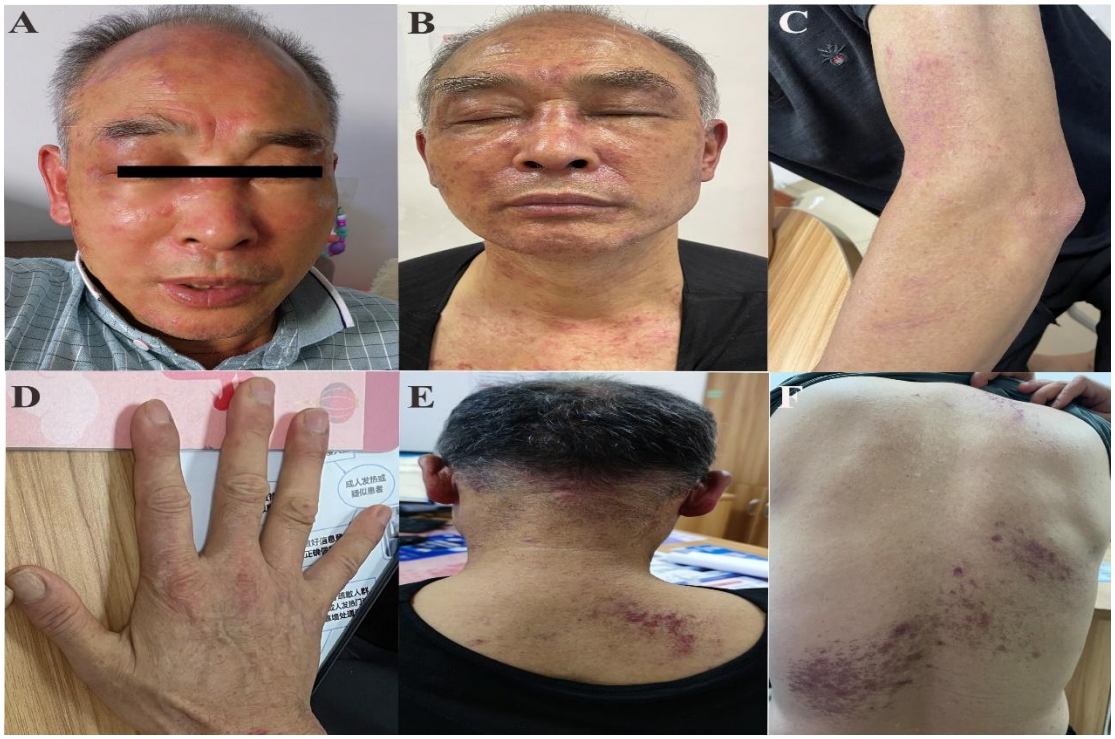

Figure 1: Skin rash in the patient: erythema on the lateral eyelid (heliotrope rash) (A), around the neck (V-neck sign) (B), on the arm (C), on the back of joints (Gottron sign) (C and D), and from the head and shoulder to the back (Shawl sign) (E and F); (A) before glucocorticoid treatment, and (B-F) after treatment.

Biopsy of the nasopharyngeal mass revealed confluent nests composed of large cells, with moderate amounts of basophilic cytoplasm, a relatively high cytoplasmic to nuclear ratio, and obvious large nuclei with mitotic

figures. Immunohistochemical tests showed that the neoplastic population was positive for cytokeratin, E-cadhesin, Epithelial Membrane Antigen (EMA), synaptophysin, and CD56. The proliferation index was measured to be approximately 70% using Ki67, confirming the neuroendocrine nature of the tumor. In-situ hybridization for EBV-RNA was strongly reactive **(Figure 2).** The mass was identified as LCNEC based on the histological and immunohistochemical features.

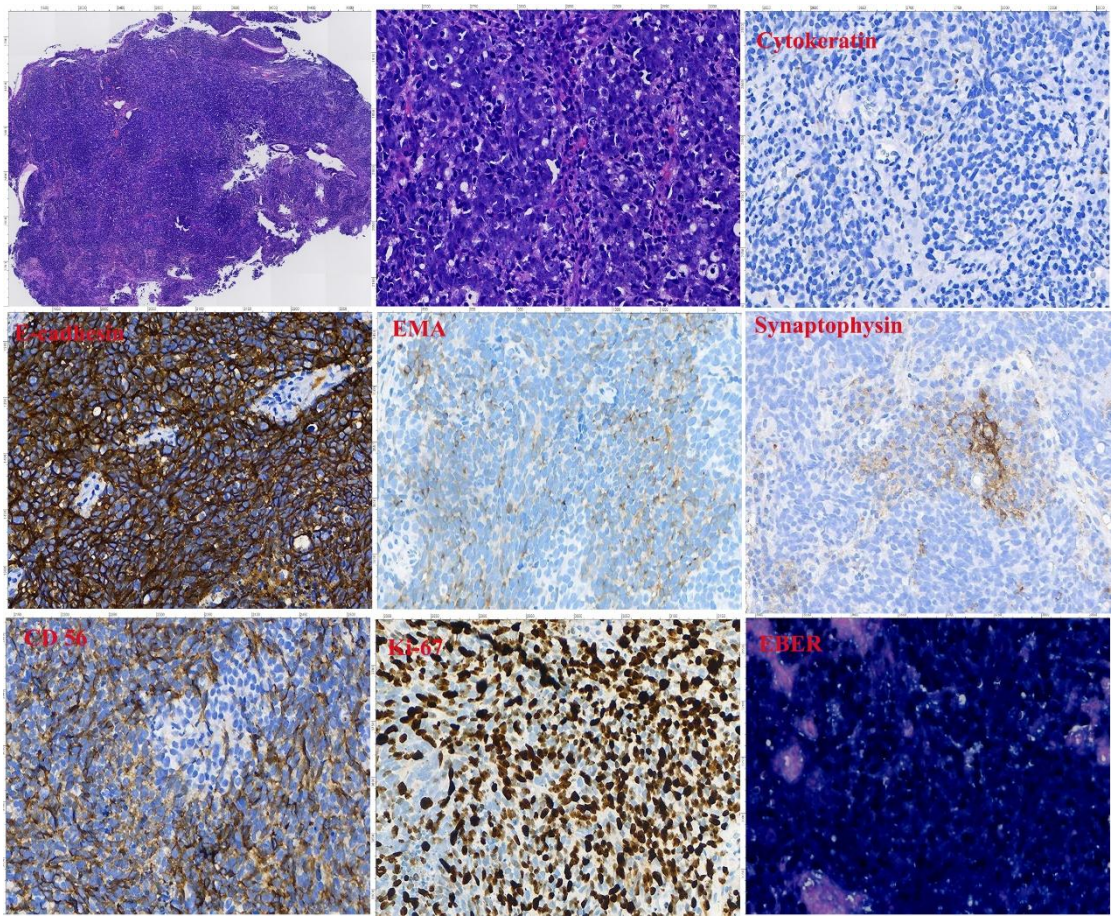

Figure 2: Immunohistochemical findings of biopsy: tumor cells with low nuclear to cytoplasmic ratio and arranged in confluent nests and sheets, positive for neuroendocrine differentiation (cytokeratin, E-cadhesin, EMA, synaptophysin and CD56) and Epstein–Barr virus-RNA.

Both fluorodeoxyglucose positron Emission Tomography/Computed Tomography (FDG-PET/CT) and ^{68}Ga-DOTATATE PET/CT demonstrated increased uptake in the nasopharynx **(Figure 3).** FDG-PET revealed muscle damage by the LCNEC near the top wall of the nasopharynx and bilateral enlarged lymph nodes in the

neck, but no distant metastasis. Serum EBV copy number test was normal, but was positive for anti-IgA antibodies. Based on the clinical manifestations, and the histological and immunohistochemical findings, the patient was diagnosed as EBV-positive LCNEC-associated dermatomyositis. Finally, he was referred to the Department of Radiotherapy.

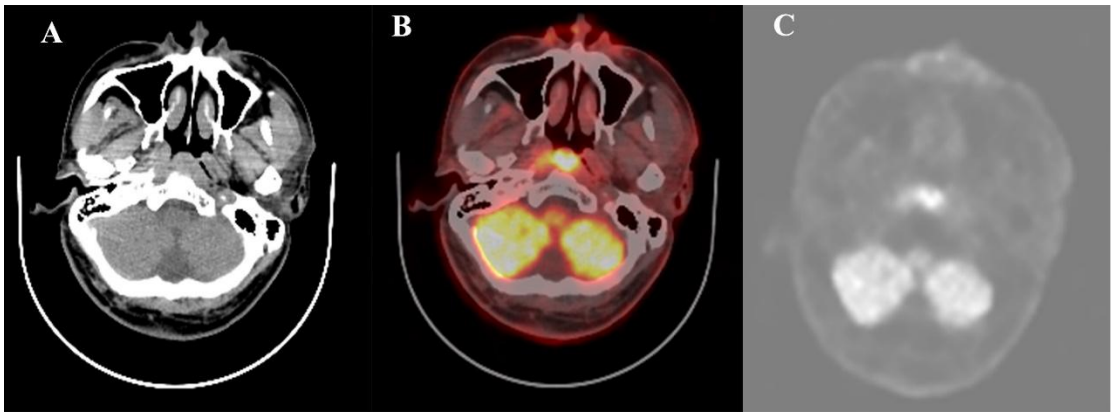

Figure 3: Computed tomography of the head and neck (A); both Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (FDG-PET/CT) (B) and ^{68}Ga-DOTATATE PET/CT (C) showed increased up-take in the nasopharynx.

Discussion

LCNEC is a unique histological entity and is formally classified as a poorly differentiated category of neuroendocrine carcinomas **[10].** Although LCNEC in lungs has been well documented, LCNEC of head and neck has only recently been added to the 4th edition of the WHO Classification of Head and Neck Tumors **[11].** The majority of LCNECs of head and neck have been described in the larynx; primary involvement of the nasopharynx is uncommon **[5].** The present case is the fifth report of an EBV-positive LCNEC arising from the nasopharynx, and the first report of dermatomyositis as the only clinical sign of malignancy. The prevalence of nasopharyngeal carcinoma is higher in China than other regions **[12].** Out of the five reported cases, including the present case, of nasopharyngeal EBV-positive LCNEC, three were from the Chinese population. All five cases were male, which highlights the predisposition of male sex for this disease. EBV infection contributes in the development of nasopharyngeal carcinoma, especially the non-keratinizing subtype **[13].** However, little is

known regarding the presence of EBV in LCNEC. Among the reported cases of LCNEC **[5-9],** only four cases have previously identified EBV infection. The exact role of EBV in the development of LCNEC needs further investigation.

The spectrum of dermatomyositis-associated malignancies varies with ethnicity and geography, and a strong association between dermatomyositis and nasopharyngeal carcinoma is well documented (pooled prevalence of 3.3% in dermatomyositis). The prevalence is extremely high in China (up to 36.5%) **[3],** which might be due to the high prevalence of EBV infection in the population. EBV can activate B cells and induce dermatomyositis as a consequence of molecular mimicry **[14].** Recently, NEC of the liver, pancreas, and prostate has been described in cases of dermatomyositis **[15-18],** with most cases seen in the liver. Piovesan et al. **[17]** reported a well-differentiated NEC associated with dermatomyositis in a 29-year-old white woman, all other patients were male with no description of the NEC categories. It is worth noting that males are predisposed to this NEC-associated disease. Herein, we have presented the first reported case of LCNEC associated CADM, a subgroup of idiopathic inflammatory myopathies characterized by cutaneous manifestations. Malignancies were diagnosed either a few months after dermatomyositis or during screening. The highest risk of malignancy was reported within the first year of dermatomyositis diagnosis **[1].** The clinical symptoms of dermatomyositis improved with the treatment of tumors along with glucocorticoids in a previous case **[17].** In the present case, dermatomyositis was the only clinal sign of LCNEC. LCNEC exhibits aggressive clinical progression with a poor prognosis, regardless of the site; the prognosis of LCNEC of head and neck remains unclear. The five-year rate of survival of patients with advanced disease is 21% **[19].** The radiosensitivity of EBV-positive nasopharyngeal carcinoma has been well established **[20].** One case report demonstrated complete clinical and radiological response in EBV-positive LCNEC after combined chemoradiation therapy, with three years disease-free survival **[7].** In our case, the rash improved partially after glucocorticoid therapy.

Conclusion

We report the first case of an extremely rare CADM associated with EBV-positive LCNEC arising from the nasopharynx. Considering the high prevalence of EBV infection and nasopharyngeal carcinoma in the Chinese, it is of great importance to screening potential malignancies in dermatomyositis of this population.

Author Contributions

SJC and GXS conceived the topic. GLS conducted the pathological analysis. YCS and YL assisted with data and figures collecting. HQL wrote the manuscript and SJC revised the manuscript critically. All authors agree to be accountable for the content of the work.

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