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Case Report

Nasopharyngeal Carcinoma Associated with Epithelioid Cell Granulomatous Reaction: a Case Report

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Abstract: We report an unusual case of marked granulomatous reaction developed both before diagnosis and after therapy in a patient with Undifferentiated Nasopharyngeal Carcinoma (UNPC).

Case Report

In December 2005 at a community hospital a 31-year-old caucasic man underwent a fine needle aspiration biopsy of an abnormal lymphadenopathy in the left-side neck. Histology showed polymorphonuclear leukocytes, necrotic debris and bizarre epithelioid cells, as well as granulomatous lymphadenitis, which raised the strong suspicion of tubercular infection. The patient then received anti-tubercular therapy with isoniazid and rifampicin for 6 months. As the suspected laterocervical node persisted, a Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) was performed showing multiple lymphoadenopathies on the left- side neck and an abnormal uptake in the nasopharynx. Left-side neck lypmpadenopathies dissection and nasopharyngeal biopsies were consequently performed. Both histological exams revealed the presence of epithelioid cell granulomas, associated with neoplastic epithelial cells.

When the patient admitted to Fondazione IRCCS Istituto Nazionale dei Tumori in June 2006, the clinical examination showed bulky bilateral cervical node involvement. The anti-tubercular therapy was discontinued. Head and neck magnetic resonance imaging (MRI) and FDG-PET were performed, showing a mass in nasopharynx with clivus, skull base, sphenoid and cavernous sinus involvement, intracranial extension and multiple pathological nodes up to supraclavicular fossa with a maximum diameter of 7 cm. Pathological retropharyngeal nodes were also present.

Pathologic second review revealed a pattern of undifferentiated nasopharyngeal carcinoma (UNPC) with secondary granulomatous reaction both in the nasopharynx biopsy specimen and in the node (Figure 1). The tumor was composed of sheets or wide bands of large undifferentiated cells with a population of non-neoplastic small lymphocytes. EBER/EBV (Epstein-Barr virus-encoded small RNAs/Epstein-Barr virus) was detected in primary tumor biopsies by in situ hybridization on paraffin-embedded tissue sections using a

fluorescein-conjugated oligonucleotide probe for EBER/EBV. According to International Union Against Cancer 2002 classification the disease has been clinically staged as T4 N3b M0, IVB. Plasma EBV DNA level that quantitatively analyzed with real-time polymerase chain reaction (PCR) was 48.743 copies/mL.

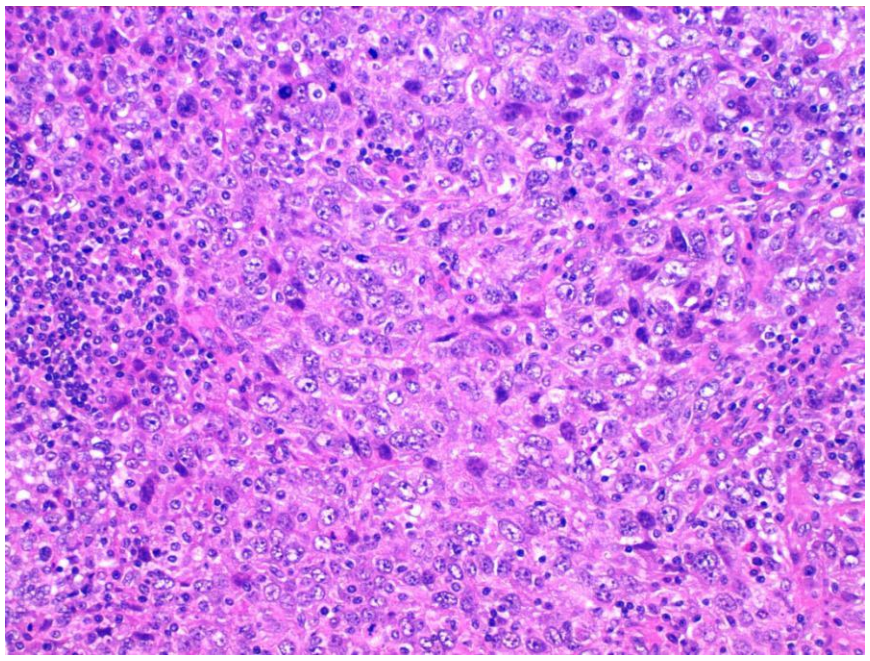

Figure 1. Section of parotid lymph nodes infiltrated by nasopharyngeal nonkeratnyzing carcinoma undifferentiated subtype (UNPC). H&E ×400

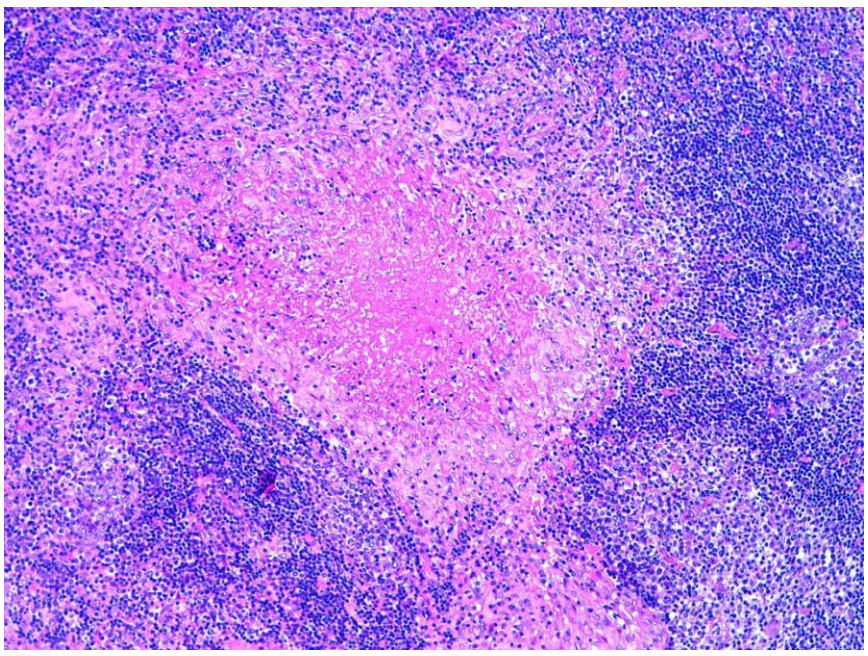

Figure 2. Same case with necrotizing granulomatous reaction. H&E ×25

Different patterns of the granulomatous lesions were observed in primary tumor and pathologic nodes. In the primary tumor the specific lesion was observed from T-cell confluent on the granulomata, with caseous and focal necrosis. The infiltrate spilled the lymphocytosis, with cytologic features similar to the small lymphoid cells occupying large and poorly demarcated masses of the epithelioid cells. In addition, specific lymphomatous infiltration and prominent granulomatous infiltrates were observed, showing a florid epithelioid and granulomatous cell reaction. The section of the cervical lymph nodes showed confluent epithelioid granulomata completely obliterating the lymphoid tissue. In fact, the histological picture may resemble granulomatous lesions similar to those seen in tuberculosis, as collections of the epithelioid cells are not uncommon.

The possible coexisting tuberculosis was searched using special stains and PCR-based assays for the identification of Mycobacterium tuberculosis; moreover, nested PCR assays for M. Tuberculosis (TB) DNA were performed on formalin-fixed, paraffin-embedded tissue, but without detecting M. Tuberculosis DNA.

Starting from June 2006, the patient received induction chemotherapy with docetaxel 75 mg/m^2 intravenous (*i.v.*), cisplatin 75 mg/m^2 *i.v.* on day 1 and 5-Fluorouracil 750 mg/m^2 per day by continuous infusion for 96 h, every 21 days, for three cycles. Following induction chemotherapy, the patient underwent Intensity-Modulated Radiation Therapy (IMRT) concurrently with 3 cycles of cisplatin 100 mg/m^2 every 21 days. A seven-coplanar-fields step and shoot technique was used. A total dose of 66 Gray (Gy) and 54 Gy was administered to high risk (HR) target volume and low risk (LR) target volume, respectively. HR target volume included primary nasopharyngeal tumor and involved lymph nodes (LNs), with 0–25 mm expansion to account for microscopical invasion; LR target volume comprehended HR-volume plus a margin of 5 mm and all uninvolved cervical nodal levels. Standard fractionation of 2 Gy was used. At the first follow-up, three months later, excellent complete clinical and radiological response was found. Plasma EBV DNA level was negative. In April 2008, an asymptomatic, solitary cervical lymph node found at ultrasonography was biopsied. Histology showed granulomatous tissue in the absence of neoplastic cells.

In October 2008, the patient had local recurrence, with radiological (MRI and FDG-PET) evidence of disease into the adjacent petrous portion, foramen lacerum, cavernous sinus, and parapharyngeal space, without evidence of cervical nodal involvement. Due to intracranial extension of disease, a confirmatory biopsy was not performed. Pattern of failure analysis showed that recurrence was marginal to the HR-target volume, in the area very close to the optic chiasm. Plasma EBV DNA level was negative. Patient received reirradiation at a total dose of 59.4 Gy with 1.8 Gy per fraction with dynamic conformal arcs, concurrently with cisplatin 100 mg/m^2 every 21 days.

In March 2011, approximately 29 months after local failure, patient had nodal failure within left parotid gland. Parotid nodes were not included in the original LR-target volume, as their involvement occurs

in only 1% of cases[1]; however, the patient had multilevel nodal disease (parotid and II level), possibly due to altered lymphatic drainage deriving from previous neck dissection. Patient received left parotidectomy with evidence of one pathological node and granulomatous necrotizing reaction (Figures 2). After a careful analysis of cumulative dose to nervous organs at risk from the two previous radiotherapy courses, a second dynamic-conformal-arcs reirradiation at a total dose of 45 Gy with fraction size of 1.8 Gy to the parotid bed was administered, concurrently with radiosensitizing cisplatin.

At the time of writing, 8 years and 6 months after diagnosis, the patient is free of disease without severe late toxicities.

Discussion

First aim of this case report is to assess clinical and histological characteristics of the association between granulomatous reaction and nasopharyngeal cancer, in order to help clinicians in avoiding potentially fatal diagnostic pitfalls and management errors.

Firstly, it is crucial to distinguish between tuberculosis (TB) and specific granulomatous reaction. In Italy[2], the incidence rate of tubercolosis is low, approximately about 5.7 cases for 100,000 people and it is mandatory to use special stains and PCR-based assays to identify the Mycobacterium tuberculosis before TB treatment.

Although epithelioid histiocyte clusters in association with cancer have been described in literature[3-6] as a paraneoplastic syndrome manifestation, massive granulomatous reactions are rare in head and neck cancer[7-8].

To our knowledge the sarcoidosis, a systemic granulomatous disease, can be located in the nasopharynx[9], yet, the association of granulomatous reaction and nasopharyngeal undifferentiated carcinoma was documented only in four cases in the world. In particularly, this associated was observed after radiotherapy[10] as inflammatory consequence to treatment.

The Epstein-Barr virus was described as the causative factor of sarcoidosis; but this association has been illustrated in relationship with other viruses[9]. EBV has been reported with granuloma reactions, however, to our knowledge EBV is not related to epithelial cancers[11-12].

This tumor-associated granuloma indicates an immune response of the tumor stromal tissue to antigens expressed by the cancer and manifests as a local T-cell-mediated reaction[13].

Due to the prominent epithelioid granulomatous response we postulate that a potential relationship exists between the specific T-cell reaction and nasopharyngeal cancer recurrence. The paraneoplastic changes in lymphnodes are caused by the partial involvement of antitumor immune response, possibly being a marker of disease. Finding of necrosis, prominent sinus histiocytosis, or prominent fibrosis of a lymph node in the absence of a history of chronic lymphadenitis or inflammation in the draining area should be considered a possible indication of nasopharyngeal cancer recurrence. The presence of a similar granulomatous reaction suggests a host-versus-tumor response and should be considered in differential diagnosis at least in areas where UNPC is endemic.

This case stresses the diagnostic difficulties encountered, because the exuberant granulomatous reaction almost hid carcinoma and resulted in delayed case management. The granulomatous reaction may also reflect a favorable host T-cell mediated immune response against cancer disease. Liu et al. showed the presence of epithelioid granulomas as associated to favorable prognosis in gastric cancer[14], but it is not clear whether granulomas in UNPC might have any prognostic significance. However, it is possible to label this reaction as an immunological response to tumor antigens that contributed to the favorable evolution, despite initial disease extension. Other investigators suggested that granulomatosis reaction can constitute a strong, favorable immunologic response against the neoplasm.

Conclusions

Granulomatous reactions related to malignancies have already been described[15-16]. This abnormal reaction, in association with tumor may cause problems in the correct interpretation of disease extension both at disease onset and in presence of tumor recurrence.

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