**Abstract.** The incidence of rhinopharyngeal carcinoma is fewer than one person per 100,000 population but it is one of the most common types of cancer in Southern China. The mechanisms often implicated suggest an important role of genetic, ethnic and environmental factors. Lung metastases are the most frequent, accounting for 66% of distant metastases. Other metastatic sites include bone (22%) and liver (10%). We report a case with breast skin and axillary nodes involvement.

Rhinopharyngeal carcinoma (RPC) is a non-lymphomatous, squamous cell carcinoma that occurs in the epithelial lining of the nasopharynx. The incidence of this neoplasm is fewer than one person per 100,000 population (1), and although it is rare in Europe and North America, it is one of the most common types of cancer in Southern China (2). Moreover, the incidence of nasopharyngeal carcinoma remains high among Chinese people who migrate to South-East Asia or North America, while in Chinese people born in North America it is lower than in those born in Southern China (3, 4). This evidence suggests an important role of genetic, ethnic and environmental factors. However, the Epstein-Barr virus (EBV) appears to be the strongest and most consistently related factor.

In fact, using the current in situ hybridization methods for the detection of EBV-encoded small RNAs (EBER), almost 100% of cases of RPC have shown EBERs in the nuclei of the tumour cells, without any dependence on the histological subtypes (5). In addition, pre-malignant lesions have been shown to harbour EBV, suggesting the occurrence of infection in early phases of carcinogenesis (5).

**Case Report**

A 58-year-old man came to our attention for laterocervical and supraclavicular lymphnode enlargement. A biopsy was performed and histology revealed the presence of metastatic rhinopharyngeal carcinoma, confirmed by total body computed tomography (CT) (Figure 1). A new biopsy of rhinopharyngeal mucosa was executed and confirming the presence of cytokeratin-positive, CD45-negative, non-keratinising rhinopharyngeal carcinoma. For this reason, the patient received conventional radiotherapy (RT) (6480 cGy to the cervical region and 5040 cGy to the supraclavicular region) associated with radiosensitising chemotherapy with mitomycin C. A complete response to treatment was obtained and regular clinical and instrumental controls were scheduled.

After four years of disease-free survival, the patient reported left shoulder pain. In November 2000, he underwent nulear magnetic resonance (NMR) imaging which showed the presence of an osteolitic lesion involving the distal left scapula destroying the coracoid process and the anterior glenoid edge; peri-skeletal pathologic tissue dislocating the deltoid and subscapular muscles and axillary lymphadenopathy (Figure 2). In addition, a total body CT showed an enlarged supraclavicular lymph node (1 cm diameter) and several osteoblastic pelvic lesions (Figure 3). The performed biopsy of the scapular bone lesion documented the presence of metastases from rhinopharyngeal carcinoma. A 21-day chemotherapeutic regimen based on the infusion of...
of epirubicin (70 mg/m²) and cisplatin (60 mg/m²) was executed for 6 cycles. Re-evaluation of the disease showed lymph nodal and bone progression. Thus a new two-week chemotherapy with adriamycin, bleomycin and vincristine (ABO) for five cycles was administered obtaining a stable bone disease and a complete response for the lymph node disease.

In May 2002, a left breast mass and several axillary nodes were clinically and echographically found. A fine-needle biopsy of the mammary lesion showed an intraductal-like breast cancer. A left mastectomy with axillary lymphadenectomy was performed. A histological evaluation revealed breast tissue free from the presence of metastases from rhinopharyngeal carcinoma, which were present instead in 10/17 axillary lymph nodes and in breast subcutis. The poor performance status allowed only palliative radiotherapy treatment to the painful left shoulder (total dose 5000 cGy), with a good control of symptoms and the radiological evidence of stable disease. A strict follow-up program was scheduled. In April 2006, the patient reported skin lesions on his left shoulder. A biopsy was performed and histology revealed the presence of rhinopharyngeal cells (Figure 4). Moreover serological tests were executed to evaluate the presence of antibodies against components of EBV. The tests were positive and the results are summarized in Table I. A new chemotherapy regimen with the association of weekly cisplatin and capecitabine was started. The patient completed all 6 cycles scheduled with acceptable general condition, a good compliance with treatment and stable disease. To date, he is still alive with a good quality of life and no evidence of progressive disease.

Discussion

RPC presents important characteristics for its unique natural behaviour, epidemiology and treatment, even more than other types of head and neck cancer. It is the third most common malignancy in Southern China and EBV is present in all poorly differentiated and undifferentiated non-keratinizing NPC (6, 7).

For many years, the standard approaches for treatment have been surgery, with or without postoperative radiotherapy for resectable disease, radiotherapy for unresectable disease and palliative chemotherapy for recurrent/metastatic disease (with methotrexate or cisplatin in combination with 5-FU or, more recently, paclitaxel) (8).

This neoplasm shows various degrees of differentiation and is frequently observed at the pharyngeal recess posteromedial to the medial crura of the Eustachian tube opening in the rhinopharynx (9). The histological classification of RPC, proposed by WHO in 1978, divides tumours into three
groups: type I, typical keratinising squamous-cell carcinomas; type II, non-keratinising squamous carcinomas; and type III, undifferentiated carcinomas (10).

An alternative classification distinguishes the tumour into two histological types: squamous cell carcinomas and undifferentiated carcinomas (11). Nowadays, the histological types of nasopharyngeal carcinoma are defined either as squamous cell carcinomas or non-keratinising carcinomas. The second group is further subdivided into differentiated and undifferentiated neoplasms (12). Undifferentiated carcinomas have lower local tumour control rates with treatments and an higher incidence of distant metastases than differentiated ones (13, 14).

Patients with rhinopharyngeal carcinoma frequently present a variety of symptoms, such as epistaxis and nasal obstruction, associated with the presence of the neoplasm. In some cases the tumour can involve the latero posterior or superior rhinopharyngeal space with dysfunction of the Eustachian tube, skull base erosion and palsy of the fifth and sixth cranial nerves. A retrospective analysis identified symptoms of RPC at presentation as neck mass (76%), nasal dysfunction (73%), aural dysfunction (62%), headache (35%) and diplopia (11%). The physical signs, at diagnosis, were enlarged neck node (75%) and cranial nerve palsy (20%). The most commonly affected cranial nerves were the third, fifth, sixth and the twelfth (15, 16).

There is no evidence of the natural behaviour and routes of extension of rhinopharyngeal carcinomas in the early stage of development; however, it is known that rhinopharyngeal tumours are associated with a high incidence of distant metastases. Lung metastases are the most frequent, accounting for 66% of distant metastases. Other metastatic sites include bone (22%), liver (10%), skin, mediastinum and bone marrow (6).

Concerning the usefulness of diagnostic methods, NMR is better than CT for discovering both superficial and deep rhinopharyngeal soft tissue and for differentiating tumour from soft tissue. NMR is also more sensitive for assessment of retro-pharyngeal and deep cervical node metastasis and in detecting marrow infiltration. These latter aspects are correlated with an increased risk of distant metastasis (17-20). However, CT should be undertaken when the status of the base and skull cannot be satisfactorily established with NMR (19). The role of positron-emission tomography (PET) in detection of distant metastases in other malignancies has been established, but its application in the staging of rhinopharyngeal carcinoma has not been defined (21). After treatment, CT and NMR have low sensitivity and moderate specificity in the detection of tumour recurrence (22). On the other hand, PET has been reported to be more sensitive than CT and NMR at detecting residual and recurrent rhinopharyngeal tumours (23).

Adjuvant radiotherapy has become a standard approach for the treatment of locally advanced resectable disease. However, the benefits of adding concomitant chemotherapy to radiotherapy in the postoperative setting have recently been confirmed in two randomized trials (24, 25). In both trials, the rate of local and regional relapse was significantly lower with a longer disease-free survival in patients receiving chemoradiotherapy compared with those receiving radiotherapy alone (24, 25). In addition, one of the trials reported a significant increase in overall survival (OS) \( \rho=0.02 \), with a 5-year estimated OS rate of 53% with chemoradiotherapy and 40% with radiotherapy (25). Moreover, a phase III study comparing standard radiotherapy with or without weekly oxaliplatin in the treatment of loco-regionally advanced disease showed an OS of 100% and a metastasis-free survival (MFS) of 92% after a median of 24 months follow-up, for patients

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**Table I. Serological markers of exposure to EBV.**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Concentration</th>
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<tbody>
<tr>
<td>VCA (viral capsid antigen) IgG</td>
<td>32 mg/dl</td>
</tr>
<tr>
<td>VCA IgA</td>
<td>80 mg/dl</td>
</tr>
<tr>
<td>EA (early antigen)</td>
<td>40/80 U/ml</td>
</tr>
<tr>
<td>EBVA or EBNA (nuclear antigen)</td>
<td>40 U/ml</td>
</tr>
</tbody>
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**Figure 4. Histological aspect of nodular skin lesion.**
receiving chemoradiotherapy (CCRT)(26). The addition of chemotherapy to radiotherapy is also a standard approach for unresectable disease (27). The platinum/5-FU infusion regimen is still considered standard for those patients with recurrent/metastatic disease who are able to tolerate it.

A large meta-analysis of trials, an update of which was reported recently (28), demonstrates the benefits to patients’ survival of adding chemotherapy to radiation therapy vs. radiotherapy alone.

A phase III trial conducted on 295 patients evaluated the efficacy of adding high-dose cisplatin to conventional single daily fractionated radiotherapy. This trial showed that radiochemotherapy, compared to radiotherapy alone, improved survival significantly (3-year projected OS 37% vs. 23%, p=0.014) (29). In another randomized study that compared conventionally fractionated radiotherapy alone or in combination with carboplatin and 5-FU, combined therapy improved both the 3-year disease-free (51% vs. 31%, p=0.02) and OS rate (42% vs. 20%, p=0.04) (30).

Despite the indisputable benefits of chemoradiotherapy in improving locoregional control and, in some cases, survival, acute toxicity is problematic. There is a significant increase in acute grade 3/4 toxicities, particularly mucositis, with chemoradiotherapy vs. radiotherapy alone (24, 25, 29, 30).

The challenge of reducing these side-effects may be supported by new promising targeted therapy. This approach aims to create more specifically directed anticancer treatment to overcome the limits of conventional cytotoxic agents.

A range of agents, with significant activity in the clinical setting and different mechanisms of action, have been developed to target the endothelial growth factor receptor (EGFR). The most studied agent in head and neck cancer is the IgG1 monoclonal antibody cetuximab (Erbitux®), which is directed against the extracellular ligand-binding site of the receptor. Gefitinib and erlotinib, EGFR tyrosine kinase inhibitors, have also demonstrated some activity. In locally advanced disease, a phase III study has shown that cetuximab enhances the activity of radiotherapy and improves survival compared with radiotherapy alone (31). In patients receiving cetuximab plus radiotherapy, the median survival was significantly prolonged by more than two years compared with radiotherapy alone (54 vs. 28 months, p=0.02). Cetuximab in combination with cisplatin-based chemotherapy, as first-line treatment, has also revealed good activity for recurrent or metastatic head and neck cancer (32). In a randomized phase III study, the response rate with cetuximab and cisplatin was 26% compared with 10% for cisplatin and placebo (p<0.05). There was also a non-significant increase in OS (9.3 vs. 8 months). The addition of cetuximab to cisplatin-5-FU combination chemotherapy in metastatic and/or recurrent disease also appears promising (33). The activity of cetuximab plus cisplatin or carboplatin in recurrent and metastatic platinum-refractory disease was confirmed by two phase II studies (33, 34). In these, response rates of 12% and 15%, and disease control rates of 28% and 54%, respectively (34, 35), were reported.

Recently, the activity of single-agent cetuximab, in a similar population, was also described. Single agent response rates are analogous to those obtained with combination therapy (cetuximab and cisplatin/carboplatin). Notably, cetuximab did not exacerbate the toxicity profiles of co-administered agents in any of the studies. The most common side-effects are skin reactions, particularly an acne-like rash. These have become an accepted characteristic side-effect of treatment with EGFR inhibitors and tend to develop in the majority of patients.

Conclusion

The management of this rare neoplasm still remains controversial. There is clinical evidence of the utility of concomitant chemo-radiotherapy both in metastatic and adjuvant setting. The encouraging results of targeted therapies support the necessity of further studies to better clarify the activity and efficacy of these new molecules, alone or in combination with conventional chemotherapy and/or radiotherapy. The aim is to obtain anticancer schedules that improve patients’ survival and quality of life reducing acute and long-term side-effects.

References