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ORIGINAL ARTICLE

Extramedullary Plasmacytoma of the Paranasal Sinuses: Combining Surgery with External Radiotherapy

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Abstract Extramedullary plasmacytomas (EMP) are rare neoplasms characterized by the proliferation of a single B-lymphoid cell clone, arising primarily in the head and neck region. The purpose of this study is to report our experience in the management of EMPs arising in the paranasal sinuses. We retrospectively reviewed clinical records of 7 patients (4 men and 3 women), admitted between 1995 and 2010 for EMPs of the paranasal sinuses—5 within the ethmoid and 2 in the maxillary sinus. Treatment consisted in endoscopic resection followed by external RT. The mean follow-up period is 50 months (range 9–67 months). Local recurrences developed in 2 out of 7 cases. Both recurrences occurred in maxillary EMPs and they underwent salvage treatment—combination of RT and surgery. At the time of analyzing these data 5 patients (70 %) were alive and two (30 %) have died of their disease. A single patient, presenting local relapse at 6 months, died due to the disease at 9 months. One patient progressed to multiple myeloma. Larger controlled clinical trials are necessary to establish an optimal treatment of choice that implies an individualized management of these patients.

Keywords Extramedullary plasmacytoma · Paranasal sinuses · Surgery · Radiotherapy · Recurrence · Outcomes

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Introduction

Plasma cell neoplasms represent a heterogeneous group of rare tumors characterized by the proliferation of a single B-lymphoid cell clone, producing a monoclonal immunoglobulin [1]. They can appear as solitary lesions (plasmacytoma) or disseminated throughout the body—multiple myeloma (MM). Plasmacytomas develop either within the marrow-containing bones (solitary bone plasmacytoma—SPB), or less often into different soft tissues (extramedullary plasmacytoma—EMP) [1–3]. The MM: SPB: EMP incidence ratio is of approximately 40:2:1 [3]. Of the 3 entities, EMP has the best prognosis.

Extramedullary plasmacytomas are localized into the upper respiratory tract in over 80 % of cases, probably due to the Mucosa-Associated Lymphoid Tissue present in this area [1–3]. It accounts for 1 % of all head and neck malignant tumors. The most common sites of EMPs are the nose, paranasal sinuses, nasopharynx and tonsils, but it can also occur in the gastro-intestinal tract, CNS, urinary bladder, thyroid, testes, parotid gland and lymph nodes [3–6]. Men are more commonly affected, with a median age at diagnosis of 50–60 years. EMP develops as a locally invasive submucosal tumor with a tendency to recur. Diagnosis depends upon biopsy and exclusion of disseminated disease (MM). EMPs have the best prognosis of all plasma cell tumors, although within 10 years 11–30 % of cases can progress toward MM [7].

Because of its infrequency and intricate diagnosis, EMPs of the head and neck still remains a challenge for the physician. Furthermore, a consensus regarding the optimal management has yet not been reached. Radiotherapy (RT) is considered by many the treatment of choice since EMPs are radiosensitive. However recent studies demonstrate better long term outcomes through a combination of RT

and surgical removal [8–11]. Surgery alone has also been proven highly efficient, provided that negative resection margins are attained [9–11].

The purpose of this study is to report our experience in the management of EMPs arising in the paranasal sinuses. Our treatment protocol consisted in endoscopic resection followed by complementary RT.

Materials and Methods

The present study has been approved by the "Iuliu Hatieganu" University of Medicine and Pharmacy Institutional Review Board. Seven patients with EMPs of the paranasal sinuses, admitted between 1995 and 2010 in our Otorhinolaryngology University Hospital, were identified. Local extension of the tumor was assessed by CT and MRI scans. Diagnosis was founded on biopsy and immunohistochemistry. MM was excluded through systematic workup including complete blood cell count, lactic dehydrogenase, calcium, phosphorus, C-reactive protein, beta2 microglobulin, erythrocyte sedimentation rate, serum and urinary protein electrophoresis with immunoassay, skeletal bone survey and bone marrow biopsy. Case records were reviewed to acquire data on demographics, clinical presentation, pathologic characteristics, treatment and results.

Patients were followed up every 2 months during the first year and then once a year. During follow-up local recurrence was ruled out by endoscopy and CT scans, whereas routine surveillance excluded MM development. Local relapse was confirmed through biopsy. The progression to MM was recognized by detection of new lytic bone lesions.

Censored observation at the last follow-up was used to compute overall survival (OS). Kaplan–Meier product limit method generated survival curves. Statistical analysis was performed by use of SPSS ver. 10.0 (SPSS Inc, Chicago, IL).

Results

Patients

Details of patients' demographics and tumor characteristics are shown in Table 1. The median age at diagnosis was 55 years, with a range of 38–71 years. The gender ratio in this study was 4:3 detrimental to male gender. The main symptoms at presentation were nasal obstruction and epistaxis, other complains were nasal discharge, swallowing, pain/tenderness of the maxillary sinus. The most frequent tumor site was the ethmoid sinus (5 cases, 71.5 %), followed by the maxillary sinus (2 cases, 28.5 %). There were no frontal or sphenoid tumors as well as no intracranial extensions.

Treatment

Tumors were removed through the endonasal endoscopic approach (ethmoidectomy for ethmoid tumors and medial maxillectomy for maxillary tumors) alluring complete resection of the lesion and the surrounding mucosa. No complications were recorded during or after surgery. One month later, patients underwent RT with a 40 Gy irradiation dose in 20 fractions. RT side effects included xerostomia in 2 patients and nasal dryness in 3 patients.

Outcome

The mean follow-up period is 50 months (range 9–67 months). Local recurrences developed in 28.5 % of patients (2 out of 7). The time from diagnosis to local recurrence was 6 and 9 months, respectively (mean 7.5 months). Both recurrences occurred in maxillary EMPs and they underwent salvage treatment– combination of RT and surgery. At the time of analyzing these data five patients (70 %) were alive and two (30 %) have died of their disease. A single patient, presenting local relapse at 6 months, died due to the disease at 9 months. One patient progressed to MM. The disseminated lesions were detected after 20 months of follow-up and the patient died 4 moths later. In our series the 3- and 5-year OS rates were 71.5 and 65 %.

Discussion

Extramedullary plasmacytomas have an estimated incidence of 0.04 cases per 100,000 individuals [8] with a noticeable predilection for the nasal cavity and paranasal sinuses. A possible explanation for this occurrence is that the lymphoid tissue associated to the upper airways suffers a chronic stimulation caused by inhaled irritants or viral infections that, in time, leads to neoplastic transformation [8, 12]. Because of its infrequency, natural history and pattern of progression, most reports are retrospective reviews and case reports [3]. We identified 7 patients diagnosed with EMP treated over a 15 years period, with a median age of 55 years. Soft tissue plasmacytoma has a significant sex-related susceptibility, with a mean male/female ratio of 2.7. In this study males were more frequently affected, consistent with data previously reported [1–15].

Extramedullary plasmacytomas progresses as a locally destructive tumor, but in 5–20 % of cases cervical lymph nodes metastasis may be present at the time of diagnosis [1].

Table 1 Treatment and outcome of patients in the present study

Age	Gender	Site	Relapse	Outcome
45	M	Maxillary	9 months Local relapse	Disease free 65 months
71	M	Ethmoid	None	Disease free 50 months
49	F	Ethmoid	None	Disease free 58 months
55	M	Maxillary	6 months Local relapse	Died 9 months
66	F	Ethmoid	20 months Multiple myeloma	Died 24 months
60	F	Ethmoid	None	Disease free 35 months
38	M	Ethmoid	None	Disease free 67 months

The clinical presentation is not specific, depending upon tumor location. The most common nasal symptoms, as confirmed by our survey, are progressive nasal obstruction and recurrent epistaxis [13, 14]. Other possible symptoms are swelling, headache, nasal discharge or proptosis [15, 16], pain usually occurs when there is bone involvement or infection.

Currently accepted diagnostic criteria for EMPs were established by Galieni et al. [17]: monoclonal plasma cell histology; bone marrow plasma cell infiltration not exceeding 5 %; normal skeletal survey results, comprising radiology of the long bones; absence of hypercalcemia, anemia or renal failure; and low serum M protein concentration, if present.

Since the tumor displays submucosal growth and the mucosa might be thickened as a result of a chronic inflammation [16], profound biopsies should be taken to avoid errors. CT, MRI and a full endoscopic examination are mandatory to determine tumor extension [9–15].

Traditionally EMP treatment has been RT. Current guidelines recommend an irradiation dose between 40 and 50 Gy in 20 fractions with a margin of 2 cm encompassing the primary tumor [9–18], with greater doses required for tumors larger than 5 cm [1, 8, 9, 14]. Soft tissue plasmacytomas are radiosensitive and regional control can be achieved in more than 80 % of the cases [7–9, 14, 19]. Complete excision of EMP is challenging due to the vicinity of vital structures and the large size of the tumor [3, 9, 14]. Moreover, surgery is frequently associated with poor functional and cosmetic results [10, 11, 15, 16]. When negative margins are attained, local control rates with surgery alone are similar with those for RT alone [3].

It has been demonstrated that a combination of surgery and RT produces better outcomes regarding long term survival: Alexiou et al. [8] firstly demonstrated that a combination of surgery and RT yielded the best 5-year survival. Sasaki et al. [9] found that patients receiving any combination of RT and surgery had meaningfully improved survival than patients submitted to RT alone or surgery alone. In the most recent review on the EMP treatment, D'Aguillo et al. [3], consistent with previously published data, found that a combination of RT and surgery is associated with the best outcomes.

Complete surgical excision of EMPs of the paranasal sinuses is certainly feasible and safe, with no esthetic consequences by using the endoscopic approach. Nevertheless resection margins are difficult to assess and thus complementary RT is recommended to ensure optimal local control.

In a recent review on EMPs, Kilciksiz et al. [23] reported 5- and 10-year overall survival rates of 71 and 69 %, and a 10-year local control rate between 73 and 100 %. Subsequent to endoscopic excision followed by a 40 Gy irradiation regimen (in accordance with current recommendations), we achieved a 5-year OS of 65 %. Our study was limited by the small number of patients and the fact that 2 cases were lost from observation at 35 and 50 months, respectively, both being disease free that time. The combined treatment permitted the decrease of the effects that RT could have on the orbit. Creach et al. [14], reported that out of 16 patients with head and neck EMP, treated with a median dose of 50.4 Gy, 2 patients (11 %) developed a radiation-induced malignancy at 6 and 7 years after treatment. Moreover, Alexiou et al. [8] demonstrated that patients receiving RT for EMP of the head and neck had a higher conversion rate to MM. Forty to 50 Gy RT for the paranasal sinuses are considered safe, yet additional studies are required to assess the predisposition of EMP patients to radiation-induced tumors.

In spite of adequate treatment, local relapses still occur in EMPs of the paranasal sinuses. In our survey 2 patients (28.5 %) presented local failure, a rate in accordance with published studies. Both cases involved EMP of the maxillary sinus, suggesting the need for a different surgical approach or higher RT doses for better local control. It has been suggested that tumors within the sphenoid or maxillary sinus are associated with a worse prognosis [23].

Disagreement occurs as to whether EMP and MM are two different illnesses or different phases of the same

disease [19]. The average progression rate to MM is likely around 23 % [21] and is associated with a poorer prognosis. Recently, Guo et al. [20] reported that in patients with EMP, large tumor size (>5 cm) and elevated β2 microglobulin (>3.5 mg/L) were significant adverse factors, affecting survival. We had one case (14.3 %) that developed MM after 20 months of follow-up. Although the risk of development into MM is increased within 2 years following diagnosis, it has been demonstrated to occur even after 15 years of disease free period [1, 3, 22], suggesting the need for a long-term follow-up. Although some authors consider that plasmacytoma converted into MM has better prognosis than classic MM [23] our patient died from the disease after 4 months despite intensive treatment. So far no tumor related factors that can predict the progression towards MM have been identified, nor hasn't prophylactic chemotherapy proven to be effective [19, 21, 23].

The role of chemotherapy in EMP treatment has not been yet established. Currently, adjuvant chemotherapy may be considered for patients with refractory or relapsed disease, and even for patients with high-risk neoplasm (high-grade tumors or tumors larger that 5 cm) [1, 13, 23]. Likewise the prophylactic treatment of the neck, either with surgery or X-ray therapy, has not been shown to improve disease outcome, therefore the treatment of a clinically negative neck is not presently recommended.

Being aware of the need for an individualized treatment for EMP, D'Aguillo et al. [3] emphasized the importance of tumor extent, site of tumor, risk for transformation to MM, and histopathology in the choice of treatment.

Conclusion

Extramedullary plasmacytomas are rare neoplasms that arise primarily in the head and neck region. They require an elaborated diagnostic workup and long term patient follow-up, within a multidisciplinary approach. Both, radiotherapy alone as well as surgical excision followed by adjuvant radiotherapy have shown high effectiveness in the treatment of EMPs. Larger controlled clinical trials are necessary to establish an optimal treatment of choice that implies an individualized management of these patients.

Conflict of interest Nothing to declare.

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