MANAGEMENT OF EXTRAMEDULLARY PLASMACYTOMA OF HEAD AND NECK

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ABSTRACT
Extramedullary plasmocytoma is an expansion of a single clone of immunoglobulin-secreting plasma cells without evidence of multiple myeloma. It is an uncommon entity that occurs usually in head and neck area. It is radiocurable at average doses while adjuvant chemotherapy is still controversial. Progression rates to multiple myeloma are lower than bone plasmacytoma. We report three cases of extramedullary plasmacytoma and through a literature review we discuss radiation modalities as well as evolutionary aspects.

KEYWORDS extramedullary plasmacytoma, radiation therapy, prognosis

Introduction
Plasmocytoma is defined as an expansion of a single clone of immunoglobulin-secreting plasma cells without evidence of multiple myeloma. Extramedullary plasmocytoma (EMP) is less common than bone plasmocytoma but has a better prognosis. It most frequently occurs in head and neck region.

Radiation therapy (RT) is the mainstay of treatment although doses and prophylactic radiation of neck nodes are still subject of debate. We report three cases of head and neck extramedullary plasmocytoma (HNEMP) with no evidence of systemic disease managed at the national institute of oncology.

Case Report 1
A 70-years-old woman who presented with a neck swelling. Physical examination discovered a firm thyroid swelling without any enlarged lymphadenopathy. Ultrasound showed an enlargement of thyroid gland with no other abnormality. Thyroid function test showed no abnormality. The antithyroid antibodies were positive in very high titers. Fine needle aspiration cytology showed a diffuse infiltration of lymphocytes with a differential diagnosis of either lymphocytic thyroiditis or a lymphoma. The patient underwent total thyroidectomy. Histopathological examination showed a diffuse infiltration of the thyroid gland by neoplastic plasma cells with stromal amyloid deposition. Immunocytochemical staining including CD138, kappa and lambda chain and immunoglobulin G (IgG) showed a light chain restriction (Kappa & IgG). A complete multiple myeloma (MM) workup was negative including skeletal imaging, myelogram, renal function and serum calcium level. No adjuvant treatment was indicated. The patient is on close monitoring every 3 months. Follow up consists on physical examination, periodic blood account and dosage of serum light chains getting for recurrence or progression to generalized disease. At 3 years follow-up, the patient showed good clinical conditions without evidence of multiple myeloma.

Case report 2
A 50-years-old man with no medical history who complained 3 months earlier from left sided nasal obstruction, occasional bleeding and rhinitis treated anteriorly as sinusitis with antibiotics and steroids without relief. Physical examination at presentation discovered a swelling on the patient’s left cheek. Nasal endoscopy showed a mass arising to the middle nasal meatus.
A 66-years-old man with no remarkable medical history who complained a painless right neck mass increasing in size during the last 3 month associated to a mild odynophagia. Examination revealed an exophytic lesion of the left palatine tonsil and an adherent non tender right level II lymph node measuring 6cm. CT (computerized tomography) of the neck evidenced large lymph nodes and a mass in the right tonsillar fossa evocating a primary tumor. The patient underwent an excisional biopsy of the tonsillar tumor and a biopsy of the node. Histological study showed an extensive infiltrate of malignant plasma cells. Chemical staining showed positivity to CD138 and restriction for kappa light chains confirming a light chain extramedullary plasmacytoma (figure 3). Lymphnode dissection was difficult as there were adherences to the skin. Multiple myeloma work up including skeletal imaging, myelogram and renal function was negative. The patient underwent radiation therapy at a dose of 40 Gy (2Gy/fraction) delivered with 6MV photon beams making a total irradiation duration of 28 days. Three months after completion of radiation therapy, MRI showed no residual tumor. The disease is in complete remission one year from treatment completion and the patient is on close monitoring.

Case report 3

A 66-years-old man with no remarkable medical history who complained a painless right neck mass increasing in size during the last 3 month associated to a mild odynophagia. Examination revealed an exophytic lesion of the left palatine tonsil and an adherent non tender right level II lymph node measuring 6cm. CT (computerized tomography) of the neck evidenced large lymph nodes and a mass in the right tonsillar fossa evocating a primary tumor. The patient underwent an excisional biopsy of the tonsillar tumor and a biopsy of the node. Histological study showed an extensive infiltrate of malignant plasma cells. Chemical staining showed positivity to CD138 and restriction for kappa light chains confirming a light chain extramedullary plasmacytoma (figure 3). Lymphnode dissection was difficult as there were adherences to the skin. Multiple myeloma work up including skeletal imaging, myelogram and renal function was negative. The patient underwent radiation therapy to oropharynx and involved nodes with two oblique 6MV photon beams at a dose of 50Gy in 25 fractions and a total treatment duration of 33 days. At three months, the tumor remained stable. During follow up, monitoring of monoclonal component showed a remarkable elevation in serum dosages of light chains 6 months after initial treatment suggesting progression to multiple myeloma although skeletal imaging didn’t show any lytic or blastic bone lesion. The patient is currently under chemotherapy: thalidomide 100mg/day per os continuously, melphalan 16.5 mg /day per os (day 1- 4) every 6 weeks and prednisone 70 mg (day1-4) every 6 weeks associated to Prophylactic Enoxaparin 40 mg daily during first 4 cycles of therapy.

Discussion

Plasmocytoma is defined as an expansion of a single clone of immunoglobulin-secreting plasma cells, resulting in an increase in serum levels of single complete or partial immunoglobulin often referred to as an “M” component [1]. In contrast to SBP, monoclonal protein is detected in serum or blood in less than 25% of cases [2]. HNEMP develops in the course of multiple myeloma or individually called solitary plasmacytoma (medullary or extramedullary location). Extramedullary plasmacytomas are located in 80% of cases in the upper airways, thyroid gland is one of the rarest sites that are affected by EMP. Nearly 50 cases of solitary plasmacytoma of the thyroid gland have been reported in the literature [3-4]. Median age at diagnosis is 55 to 65 years. There is a male predominance with a sex ratio of 1.87 and a median age of 60 years [5].

Diagnosis is made in presence of a single lesion histologically confirmed without systemic involvement. Histology shows a monoclonal plasma cell infiltrate in soft tissue with no evidence of B cell component. Thus immunochemistry using CD138, CD20 and PAX5 is useful. Workup should include a negative skeletal imaging (absence of lytic bone lesions) and normal bone marrow biopsy presenting less than 10% of monoclonal plasma cells, serum free light chain assay or minimally elevated serum monoclonal protein (IgG <3.5 g/dL, IgA <2.0 g/dL) and urine monoclonal kappa or lambda <1.0 g per 24 hours) [6-7]. Head and neck plasmacytoma responds well to local therapies such as surgery and radiotherapy. Definitive radiotherapy allows optimal local control without causing significant functional impairment unlike surgery, which makes radiation therapy the standard treatment for HNEMP. Almost all studies agree that surgery alone, even if complete excision can be achieved, should not be the treatment of choice [8]. Association of surgery to RT does not seem to influence survival. In a multi institutional analysis, Sazaki et al didn’t report a significant difference in local control between patients treated with both surgery and radiotherapy versus radiotherapy alone in patients with tumor size less than 3 cm (5-year OS of 76% vs 73% ) [9]. Conversely, in presence of bulky tumor, there is high risk of local failure and it is still questionable whether single modality of radiotherapy could achieve local control and more importantly prolong survival or combination of both radiotherapy and surgery is required. This should be further investigated in surveys with bigger number of patients. Post operative radiotherapy may be indicated if incompletely excised lesion.

Our first patient underwent a complete excision of the tumor so decision was not to add any further treatment. However, in the second patient, the tumor was incompletely removed and therefore had adjuvant radiotherapy. Treatment achieved complete response at MRI realized three months after completion of treatment. Surgery was difficult in the last patient, as he had large fixed lymphnodes. He underwent a definitive radiotherapy. In presence of bulky tumor a high dose was delivered (50 Gy; 2Gy / fr). Nevertheless, he progressed 6 months after treatment to multiple myeloma which highlights the bad prognosis of bulky tumors. Studies have shown excellent local disease control and disease free survival following radiotherapy. In contrast to SBP, is curable with radiation therapy with lower rates of
progression to multiple myeloma and a 10 years survival of 72% [5] and 78% [10] in the two largest series. Debate is raised on the optimal radiation dose and requirement for elective nodal irradiation.

There are few data that support specific guidelines regarding radiation treatment volumes. According to the guidelines published in British Journal of Haematology, the target volume should include the macroscopic tumor with a margin of at least 2 cm [11]. Coverage of cervical lymphnodes is topic of discussion as it results in a significant increase in the rate of complications, mainly xerostomia. In addition, several studies reported very low rates of regional node failure [12, 13, 14, 15, 16]. Therefore, it is recommended to treat the primary tumor covering the invaded cervical nodes. Some authors recommend RT coverage to the draining lymphnodes if the primary disease involves a lymphatic structure (lymph nodes, or Waldeyer’s ring) [15,16,17]. No one of our patients had prophylactic node irradiation. The last patient received radiotherapy only to the involved nodes. The local control of HN EMP is dependent on the dose delivered to the CTV [18]. Few series attempt to establish a dose effect relationship. In a series of 17 patients treated between 1979 and 2003, Tournier-Rangeard et al found a five year local control of 90% for patients treated with doses ≥ 40 Gy compared with 40% for those who received <40 Gy (p=0.031) and no statistical difference for local control in patients treated with a higher doses versus 40 Gy (p=0.39). Radiation doses were also found to influence disease-specific survival [18]. Five year survival rates for patients who received ≥ 45Gy or < 45Gy were 87.5% and 37.5% respectively (p=0.056). Five year disease free survival was 64.1% overall.

Similarly Mendenhall et al. [15] reviewed 81 patients and reported a local control rate of 94% when the dose delivered to the CTV exceeded 40 Gy and a rate of 69% with doses less than 40 Gy. Guidelines recommend a dose range of 40 to 50 [11].

Adjuvant chemotherapy in bulky or high histological grade tumors may improve local control and prevent progression to multiple myeloma. In most series, chemotherapy didn’t impact local control or progression to myeloma. Chemotherapy in Holland and al series delayed progression to myeloma but didn’t impact its incidence [20]. One randomized trial tested adjuvant melphalan during 3 years following RT in HN EMP reported a progression rate of 12Follow up should include periodic blood counts, reimaging preferably with MRI that is realized 6 to 8 weeks after treatment and monitoring of M component gating for systemic disease prior to symptoms [22, 7]. Delayed side effects mainly xerostomia are rarely observed with radiation therapy doses in HNEMP but must be gated especially if large volume of parotid and submandibular glands is covered. Prognostic factors are age, subclinical bone disease diagnosed at spinal MRI, suppression of normal immunoglobulin and persistence of monoclonal immunoglobulin after treatment. Some reflect the presence of occult myeloma and predict progression to generalized disease. Anaplastic plasmacytoma and expression of high level of angiogenesis are pathologic features associated to bad prognosis. In the same way, bulk is an unfavorable factor associated to a high local failure rate [22]. Unlike SBP which progresses to MM in nearly 60

Conclusion

Extramedullary plasmocytoma is a rare radiocurable malignancy. Radiation therapy is the standard treatment for head and neck EMP. Moderate doses delivered to involved fields achieve local control. Survival depends on local control and progression to multiple myeloma.

Take home messages

- Extramedullary plasmocytoma occurs in the upper airways in 80% of cases.
- Radiotherapy is the standard treatment for head and neck EMP.
- The dose to the target volume is significantly related to local control and survival. Guidelines recommend a dose range of 40 to 50 Gy.
- Bulk, high grade, subclinical disease and suppression of normal immunoglobulin are factors associated to bad outcome.
- EMP has a better prognosis than bone plasmacytoma with lower rates of progression to multiple myeloma.

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Competing Interests

Written informed consent obtained from the patient for publication of this case report and any accompanying images.

References

1. Wagner Cotran RS. Robbins Pathologic Basis of Diseases. Robbins SL and Kumar V , eds. 5th ed., W.B. Saunders Company, 1994.
2. British Committee for Standards in Hematology. Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma. British Journal of Hematology 2004 ;(124):717-726.
3. Shimaoka K, Gailani S, Tsukada Y, Barcos M. Plasma cell neoplasm involving the thyroid. Cancer 1978; 41(3): 1140-1146.
4. Aozasa K, Inoue A, Yoshimura H, Miyauchi A, Matsuzuka F, Kuma K. Plasmacytoma of the thyroid gland. Cancer 1986; 58(1): 105-110.
5. Oszahin M., Tsang R.W. et al. Outcomes and Patterns of failure in solitary plasmacytoma: a multicenter rare cancer network study of 258 patients. International Journal of Radiation Oncology 2006; (64): 210-217.
6. Durie BG, Kyle RA, Belch A, et al. Myeloma management guidelines: a consensus report from the scientific advisors of the International Myeloma Foundation. Hematol J 2003; (4): 379-398.
7. Wilder RB, Ha CS, Cox JD, et al. Persistence of myeloma protein for more than one year after radiotherapy is an adverse prognostic factor in solitary plasmacytoma of bone. Cancer 2002; (94):1532-1537.

8. David Knobel, Abderrahim Zouhair, Richard W Tsang, Philip Poortmans, Yazid Belkacémí, Michel Bolla, Fazilet Dinbás Oner, Christine Landmann, Bernard Castelain, Mahmut Ozsahin. Prognostic factors in solitary plasmacytoma of the bone: a multicenter Rare Cancer Network study. BMC Cancer 2006: 6-118.

9. Sasaki R, Yasuda K, Abe E, Uchida N, Kawashima M, Uno T, Fujinawa M, Shioyama Y, Kagami Y, Shibamoto Y, Nakata K, Takada Y, Kawabe T, Uehara K, Nibu K, Yamada S. Multi-institutional analysis of solitary extramedullary plasmacytoma of the head and neck treated with curative radiotherapy. Int J Radiat Oncol Biol Phys. 2012; (2):626-34.

10. Galieni P, Cavo M, Pulsoni A, et al. Clinical outcome of extramedullary plasmacytoma. Haematologica 2000; (85): 47-51.

11. M. Hughes, R. Soutar, H. Luraft, R. Owen, J. Bird. Guidelines on the diagnosis and management of solitary plasmacytoma of bone, extramedullary plasmacytoma and multiple solitary plasmacytomas: 2009 update.

12. Mendenhal W, Mendenhal C, Mendenhal N. Solitary plasmacytoma of bone and soft tissues. Am J Otolaryngol 2003; (24): 395–9.

13. Sautar R. Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma. BJH 2004;124:717-26.

14. Mayr NA, Wen BC, Hussey DH, et al. The role of radiotherapy in the treatment of solitary plasmacytomas. Radiother Oncol 1990;17:293-303.

15. Harwood AR, Knowling MA, Bergsagel DE. Radiotherapy of extramedullary plasmacytoma of the head and neck. Clin Radiol 1981; (32): 31-36.

16. Knowling MA, Harwood AR, Bergsagel DE. Comparison of extramedullary plasmacytomas with solitary and multiple plasma cell tumors of bone. J Clin Oncol 1983; (1): 255-262.

17. Tsang RW, Gospodarowicz MK, Pintilie M, et al. Solitary plasmacytoma treated with radiotherapy: impact of tumor size on outcome. Int J Radiat Oncol Biol Phys 2001; (50): 113-120.

18. Tournier-Rangeard L, Lapeyre M, Graff-Caillaud P, Mege A, Dolivet G, Toussaint B, Charra-Brunaud C, Hoffstetter S, Marchal C, Peiffert D. Radiotherapy for solitary extramedullary plasmacytoma in the head-and-neck region: A dose greater than 45 Gy to the target volume improves the local control. Int J Radiat Oncol Biol Phys. 2006; 64(4):1013-1017.

19. Mendenhall CM, Thar TL, Million RR. Solitary plasmacytoma of bone and soft tissue. Int J Radiat Oncol Biol Phys 1980; (6): 1497–1501.

20. Holland J, Trenkner DA, Wasserman TH, et al. Plasmacytoma: Treatment results and conversion to myeloma. Cancer 1992; (69): 1513–1517.

21. Aviles A, Huerta-Guzman J, Delgado S, et al. Improved outcome in solitary bone plasmacytoma with combined therapy. Hematol Oncol 1996; (14):111-117.

22. Chang MY, Shih LY, Dunn P, et al. Solitary plasmacytoma of bone. J Formos Med Assoc 1994; (93): 397-402.

23. Bachar G, Goldstein D, Brown D, et al. Solitary extramedullary plasmacytoma of the head and neck: long-term outcome analysis of 68 cases. Head Neck 2008; (30):1012-1019.