CASE REPORT

Rhinology, 46, 153-155, 2008

Paraneoplastic refractory hypercalcemia due to advanced metastatic esthesioneuroblastoma*

Subhash Sharma, Wael Lasheen, Declan Walsh

The Harry R Horvitz Center for Palliative Medicine, The Cleveland Clinic Taussig Cancer Center, Cleveland, OH, USA

SUMMARY

Esthesioneuroblastoma (ENB) is a rare malignant neoplasm arising from the olfactory neuroepithelium. ENB has no distinctive clinical picture, but often presents as chronic unilateral nasal obstruction or epistaxis. It has a long natural history; the 5-year survival rates have been estimated at 82%. A number of paraneoplastic syndromes have been described in the setting of ENB. Humoral hypercalcemia of malignancy (HHM) has never been described with ENB before.

We describe a case of Kadish Stage C ENB with recurrent Hypercalcemia. The hypercalcemia became refractory to therapy and was the cause of death.

Key words: esthesioneuroblastoma, hypercalcemia, paraneoplastic syndrome

INTRODUCTION

Esthesioneuroblastoma (ENB) is a rare malignant neoplasm arising from the olfactory neuroepithelium [1]. ENB represents 3% of all malignant nasal tumours; it is locally aggressive with occasional metastasis. The disease has been reported in all ages; it seems slightly more common in males [2]. Since it was first described by Berger et al. in 1924, about 1000 cases have been identified. ENB has no distinctive clinical picture, but often presents as chronic unilateral nasal obstruction or epistaxis [2].

Standard diagnostic testing includes histological and immunohistochemical examination [3], contrast-enhanced computed tomography (CT) scan [4], and enhanced magnetic resonance imaging (MRI) (5). Kadish [6] proposed a staging system depending on the extent of disease; a TNM staging system was subsequently devised by Biller et al. [7] and later modified by Dulguerov [8]. The cornerstone of treatment is surgical resection. Local recurrence following initial resection occurs in 20-40% and distant recurrence in 8% [4]. Radiotherapy is then employed to help extend survival or for palliation [3]. The role of chemotherapy is less defined but it is usually reserved for Kadish stage C and recurrent disease. Chemotherapeutic agents used as single agents or in combinations include: 5-flurouracil, cis-platinum, cyclophosphamide, doxorubicin, methotrexate, nitrogen mustard, and vincristine [9,10].

ENB has a long natural history; the 5-year survival rates have been estimated at 82% [2]. Poor prognostic factors include: age > 50 years at presentation, female gender, extent of disease (Kadish staging), and recurrent disease [8]. In one study cervical lymph node involvement had a 2-year survival rate of 0% [11]. Hypercalcemia is a common complication in many advanced cancers developing in 5% of those with solid tumours and up to 33% of persons affected by multiple myeloma [12], but has never been reported in ENB. We describe a case of Kadish Stage C ENB with recurrent hypercalcemia. The hypercalcemia became refractory to therapy and was the cause of death.

CASE REPORT

A 52-year-old smoker presented with a swelling over the left glabellum. He was found to have a large mass involving the ethmoid and frontal sinuses with direct extension into the left frontal cerebral lobe on MRI. Biopsy was followed by severe bleeding. The diagnosis of ENB was clinically suspected but at that time unproven by immunohistologic studies. He then received two courses of chemotherapy involving cyclophosphamide and vincristine. This was accompanied by radiation therapy to the face, head, and neck for a total of 6144 cGy. A repeat MRI three months later showed local tumour progression. A CT-guided stereotactic biopsy of the left frontal lobe mass confirmed the presence of metastatic disease. He was given a radiation boost to the face, head, and neck with good response on follow up MRI. He was assessed five months later for definitive tumour resection but declined surgery.

Three months after that a solitary enlarged lymph-node in the jugulo-digastric region was found to contain metastatic disease and confirmed to be ENB on needle aspiration and cytology. Right selective node dissection was performed and was followed by post-operative radiotherapy to the right and left lateral head and neck and bilateral supra-clavicular areas for a total

*Received for publication: July 31, 2007; accepted: September 21, 2007

of 6000 cGy. The left neck mass disappeared. One year later a follow up chest x-ray and subsequent chest CT-scan revealed a right upper lobe lung mass along with paratracheal and hilar adenopathy. He received two courses of VP-16 and cis-platinum with partial response. This was followed by radiation therapy for a total of 5919 cGy to the chest and mediastinum which was completed six months after the discovery of the lung mass. Six month after that he developed a massive malignant hemorrhagic right pleural effusion that was treated with chest tube drainage and pleural sclerosis with interferon. This recurred a month later and he then underwent pleuroscopic drainage.

At that time he developed symptomatic hypercalcema (corrected serum calcium = 12.7 mg/dl; normal 9 -10.3 mg/dl) and was treated with forced saline diuresis, subcutaneous calcitonin, and intravenous gallium nitrate. Alkaline phosphatase was only slightly elevated. During hospitalization the patient complained of backache and an MRI of the entire spine ruled out spinal metastasis; consequently a radionucleotide bone scan was not done. Three months later the hypercalcemia recurred. He remained ambulatory and with a satisfactory quality of life except during the recurrent episodes of hypercalcemia. Serum creatinine remained normal throughout the hypercalcemic episodes. He required treatment (both outpatient and inpatient) at 7-10 days intervals with mithramycin, gallium nitrate, disodium pamidronate and calcitonin on different occasions with good response. During exacerbations the corrected serum calcium levels ranged between 14 and 19 mg/dl. This continued for a further four months. He was then admitted for the last time with another episode of severe symptomatic hypercalcemia. Serum parathormone (PTH) at that time was 5 pg/ml (normal 10-60 pg/dl). On this occasion, the hypercalcemia did not respond to aggressive saline diuresis, frusemide, disodium pamidronate, and calcitonin. He progressively became more somnolent, then comatosed and died.

DISCUSSION

Hypercalcemia has not been described with ENB previously. In advanced cancer hypercalcemia requires prompt treatment if patients are symptomatic, provided they have a good performance status and a likely survival of at least a few months [12]. Although the patient had metastatic disease he had maintained a good performance status and quality of life until the onset of hypercalcemia. This appeared to be the cause of death and therefore a significant factor in the natural history of this rare disease. Malignancy and Primary Hyperparathyroidism (PHPT) are the commonest causes of hypercalcemia; however PHPT is a very rare cause of hypercalcemia in cancer [13]. Consequently some suggest PTH assessment, in cancer, if hypercalcemia is resistant to treatment.

In this case, the origin of hypercalcemia could not be definitely determined; a low PTH level excluded ectopic PTH production or concomitant primary hyperparathyroidism. The negative whole spine MRI makes widespread bone metastasis unlikely. Although the presence of bone metastases could not be ruled out, humoral hypercalcemia of malignancy (HHM) accounts for 80% of cancer-related hypercalcemia and was the likely cause [14]. HHM is thought to be secondary to ectopic secretion of parathyroid hormone related protein (PTHrP) by malignant tumours. PTHrP may have originated from the locally recurrent ENB or distal metastasis (such as from the lung), however in practice the exact origin was of little consequence. PTHrP causes hypercalcemia via an increase in bone resorption and calcium renal retention. It is usually diagnosed clinically, but PTHrP levels are invariably elevated [14]. This paraneoplastic syndrome has been described in other malignancies [14].

Paraneoplastic syndromes are defined as tumour effects occurring at sites remote from both the primary tumour and its metastases. They occur in less than 15% of malignancies, but their effects are sometimes more disabling than the tumour. They may precede, coexist or follow the onset of the primary tumour and often have an unpredictable course [15]. Paraneoplastic syndromes may involve any organ system (such as endocrine, nervous, skin), but only endocrine syndromes have been described with ENB. The pathophysiology is usually secondary to ectopic peptide hormone production. Generally, the commonest endocrine paraneoplastic syndromes are Cushing's syndrome, hypercalcemia (including HHM), and the syndrome of inappropriate antidiuretic hormone release (SIADH). Recognition of paraneoplastic syndromes is important because they may be the first sign of an underlying malignancy and initiate a focused search allowing earlier diagnosis, while the severity of the syndrome may be used as a prognostic indicator [15].

CONCLUSION

This is the first time hypercalcemia has been described as a complication of ENB - a rare complication of a rare tumour. ENB is a neuroendocrine tumour that has been associated with a number of endocrine paraneoplastic syndromes: Cushing's syndrome, catecholamine production, and SIADH [16-18]. The presence of endocrine and metabolic abnormalities, such as hypercalcemia, in the setting of ENB should direct the physician to assess the patient for the presence of a paraneoplastic syndrome. HHM may be an important adverse prognostic indicator, as in other malignancies [19], having serious implications for diagnosis, prognosis, and treatment decisions in ENB.

ACKNOWLEDGEMENT

The Harry R. Horvitz Center is a World Health Organization Demonstration project in palliative medicine.

REFERENCES

1. McCormack LJ, Harris HE. Neurogenic tumors of the nasal fossa. JAMA. 1952; 157: 318-321.

2. Broich G, Pagliari A, Ottaviani F. Esthesioneuroblastoma: A general review of the cases published since the discovery of the tumour in 1924. Anticancer Res. 1997; 17: 2683-2706.
3. Du ZM, Li YS, Wang BF. Electron microscopic and immunohistochemical findings in a case of olfactory neuroblastoma. J Clin Pathol. 1993; 46: 83-85.
4. Oskouian RJ Jr, Jane JA Sr, Dumont AS, Sheehan JM, Laurent JJ, Levine PA. Esthesioneuroblastoma: Clinical presentation, radiological, and pathological features, treatment, review of the literature, and the university of virginia experience. Neurosurg Focus. 2002; 12: e4.
5. Schuster JJ, Phillips CD, Levine PA. MR of esthesioneuroblastoma (olfactory neuroblastoma) and appearance after craniofacial resection. Ajnr: Am J Neuroradiol. 1994; 15: 1169-1177.
6. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer. 1976; 37: 1571-1576.
7. Biller HF, Lawson W, Sachdev VP, Som P. Esthesioneuroblastoma: Surgical treatment without radiation. Laryngoscope. 1990; 100: 1199-1201.
8. Dulguerov P, Calcaterra T. Esthesioneuroblastoma: The UCLA experience 1970-1990. Laryngoscope. 1992; 102: 843-849.
9. McElroy, Edwin A. Jr. MD; Buckner, Jan C. MD; Lewis, Jean E. MD Chemotherapy for Advanced Esthesioneuroblastoma: The Mayo Clinic Experience. Neurosurgery. 1998; 42: 1023-1027.
10. Polonowski JM, Brasnu D, Roux FX, Bassot V. Esthesioneuroblastoma. Complete tumor response after induction chemotherapy. Ear Nose Throat J. 1990; 69: 743-746.
11. Koka VN, Julieron M, Bourhis J, et al. Aesthesioneuroblastoma. J Laryngol Otol. 1998; 112: 628-633.
12. Nelson KA. Walsh D. Abdullah O. McDonnell F. Homsi J. Komurcu S. LeGrand SB. Zhukovsky DS. Common complications of advanced cancer. Sem Oncology. 2000; 27: 34-44.
13. Pecherstorfer M, Brenner K, Zojer N. Current management strategies for hypercalcemia. Treat Endocrinol. 2003; 2: 273-292.
14. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. New Eng J Med. 2005; 352: 373-379.
15. Agarwala SS. Paraneoplastic syndromes. Med Clin N-Am. 1996; 80: 173-184.
16. Takahashi H, Wakabayashi K, Ikuta F, Tanimura K. Esthesioneuroblastoma: a nasal catecholamine-producing tumor of neural crest origin. Demonstration of tyrosine hydroxylase-immunoreactive tumor cells. Acta Neuropathologica. 1988; 76: 522-527.
17. Arnesen MA, Scheithauer BW, Freeman S. Cushing's syndrome secondary to olfactory neuroblastoma. Ultrastruc Pathol. 1994; 18: 61-68.
18. Myers SL, Hardy DA, Wiebe CB, Shiffman J. Olfactory neuroblastoma invading the oral cavity in a patient with inappropriate antidiuretic hormone secretion. Oral Surg, Oral Med, Oral Pathol. 1994: 77: 645-650.
19. Sakata J, Wakai T, Shirai Y, Sakata E, Hasegawa G, Hatakeyama K. Humoral hypercalcemia complicating adenocarcinoma of the sigmoid colon: report of a case. Surg Today. 2005; 35: 692-695.

Declan Walsh, Msc, Facp
The Harry R Horvitz Center For Palliative Medicine
The Cleveland Clinic Foundation
9500 Euclid Ave. – M76
Cleveland, OH 44195
USA

Tel: +1-216-444-7793
Fax: +1-216-445-5090
E-Mail: Walsht@Ccf.Org
Website: http://www.clevelandclinic.org/palliative