

Numb Chin Syndrome in Multiple Myeloma Patients: A Harbinger of Ominous Prognosis: Case Series and Review of Literature

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Abstract

Numb chin syndrome (NCS), or mental nerve neuropathy, is a sensory neuropathy of the mental nerve and is characterized by hypoesthesia, paresthesia, or a numbness sensation of the chin and lower lip. NCS is caused by multiple etiologies including cancer invasion. We present a case series of three multiple myeloma patients with NCS where the jaw symptoms are a manifestation of disease relapse with extra-medullary myeloma infiltration, including soft tissue plasmacytoma involving the mental nerve noted along the jaw bone. The soft tissue plasmacytoma was detected using magnetic resonance imaging (MRI), which is the preferable diagnostic imaging technique to evaluate this type of problem. Furthermore, we found that in all cases, the involved immunoglobulin was IgA. This is interesting because IgA is the main immunoglobulin secreted by salivary glands. In addition, it seems that NCS could serve as one of the ominous prognostic factors in these patients.

Keywords: Paresthesia; Neuropathy; Metastatic; Malignancy; MRI

Abbreviations: NCS: Numb Chin Syndrome; MNN: Mental Nerve Neuropathy; MM: Multiple Myeloma; MRI: Magnetic Resonance Imaging; SAS: Statistical Analysis System; ASCT: Autologous Stem Cell Transplantation; (Hyper-CVAD): Hyper-Fractionated Cyclophosphamide Vincristine Doxorubicin And Dexamethasone, CT: Computerized Tomography; GI: Gastrointestinal; Ig: Immunoglobulin

Introduction

Numb chin syndrome (NCS) is a neuropathy of the mental nerve caused by pinching, depression, infiltration, or disruption of the nerve fibers caused by trauma, inflammation or the pressure of a local or systemic benign or malignant tumor [1-3]. Iatrogenic procedures such as implant positioning, overextended or overfilled root canal therapies as well as trauma to the mandible have also been implicated [4]. Bone metastases from breast, prostate, lung, or hematological malignancies such as myeloma, lymphomas and leukemias have also been associated with this condition [5]. NCS may serve as the first manifestation of metastatic malignancy, tumor progression, and/or intraoral lesions [3,6].

Multiple myeloma (MM) is a systemic disease characterized by malignant transformation of plasma cells, secretion of monoclonal immunoglobulins, and bone lytic lesions [6,7]. Involvement of the jaw bone could be seen in up to 15% of MM patients [7-9]. The manifestation of such involvement can result from mass effect and compression of the mandibular nerve or its tributaries, causing numbness and pain [8,9]. Infiltration of plasma cells into the inferior alveolar canal can also cause NCS

Although the punched-out bony lesions are almost characteristic of MM, only a few reports have associated this condition with NCS. The most common cranial nerve affected by MM is the 6th cranial nerve, which occurs in 60% of these cases, next in frequency being the 8th cranial nerve, followed by the trigeminal [10,11]. This syndrome is a relatively common clinical manifestation of neoplasms metastatic to the mandible, although the incidence in MM patients is unknown [9].

The purpose of the present study is to describe 3 cases of MM infiltrating the mental nerve, a branch of the sensory trigeminal nerve, thus causing paresthesia along the mental nerve distribution

accompanied by hyperalgesia and hyperesthesia of the retro-molar region. Furthermore, we have systematically reviewed the literature on mental nerve paresthesia caused by MM.

Methods

The case series portion of this study was carried out at the University of Florida in Gainesville, Florida, USA. We performed a search of the English literature to identify all reported cases of MM presenting with NCS. Publications were searched primarily using the PubMed (<http://www.ncbi.nlm.nih.gov/>) database using the words: 'multiple myeloma', 'myeloma', 'numb chin syndrome', 'paresthesia', and 'mental nerve neuropathy'. A manual search was conducted using the reference section of relevant publications. Selection was limited to publications that specifically identified patients as having MM and symptoms of hypoesthesia, paresthesia, or a numbness sensation of the chin and/or lower lip, which could also be diagnosed as Numb Chin Syndrome. Data that included age, sex, laboratory results, imaging techniques and results, and status of MM were obtained. Analyses were performed in Statistical Analysis System (SAS) 9.4 (SAS Institute, Cary NC) software.

Case 1

A 71-year old Hispanic female was referred by her hematologist to the Oral Medicine Clinic for the evaluation of two week duration of loss of sensation on her right chin area with episodes of severe sharp pain lasting a few seconds. The patient was diagnosed with IgA

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kappa multiple myeloma stage IIIA about 10 months prior to her current symptoms and treated with lenalidomide, bortezomib and dexamethasone without response and then hyper CVAD followed by ASCT. At diagnosis, she had complex cytogenetics abnormalities and deletion of chromosome [13]. Her right chin symptoms developed within less than 2 months from her autologous stem cell transplant (ASCT). The oral examination was significant for paresthesia of the left mandible innervated by the left mental nerve. The oral cavity appeared to be normal, however, palpation of the right retro molar area triggered a significant pain that lasted for 15 seconds.

On cone beam computed tomography imaging using the iCAT (Imaging Sciences Intl., Hatfield, PA, USA), the right hemi-mandible demonstrated loss of cortical definition of the mental foramen as a prominent feature, with the opening appearing to merge with a relatively wider area of irregular but well-defined osteolysis. Thinning of the cortices of the right mandible was noted. The patient died within 1.5 months of the diagnosis of the NCS during treatment of her MM relapse.

Case 2

A 70-year old white male with a diagnosis of IgA kappa MM stage IIIA, was treated by revlimid and low dose dexamethasone followed by an ASCT. Three and a half years later he presented with sudden onset of numbness of his left chin that has persisted for several days. The pain was described as “annoying and throbbing”. He ranked his pain as a 2 on a scale of 0 to 10 with very little improvement from gabapentin. On examination, there were deficits with the cranial nerve 5, specifically the left inferior alveolar nerve. There was decreased sensation from the left commissure of his mouth to approximately 1 cm across the midline of his lower lip extending to the posterior mucosal portion of the lip.

A panoramic radiograph and a computed tomography (CT) study did not demonstrate a clear etiology and was reported as normal. MRI of the head demonstrated an infiltrating process in the mandible, primarily within the marrow space of the mandible but clearly infiltrating the course of the left inferior alveolar nerve. The marrow on the right side was abnormal; however, it was difficult to determine if the right-sided findings were a normal variation. The overall picture suggested diffuse mandibular marrow space involvement with myeloma, left greater than right. The patient received radiation and systemic therapy, but died 15 months post-diagnosis of NCS.

Case 3

A 72-year old white female with a 4-year diagnosis of IgA kappa light chain multiple myeloma stage IIA presented with numbness on her left chin. The numbness started on the right side of her chin while in remission, sensations were intermittent, but more recently had experienced numbness on her left lower jaw down to the middle of her chin. Upon extra-oral examination, a hard subcutaneous bony expansion (0.5 centimeter in diameter) was palpated on the left temporal area. A 5-6 mm thick fibrous tissue with white suppuration and pseudo pocket formation was noted in the site of the last molar.

A panoramic radiograph and CT scan did not demonstrate a clear etiology. MRI revealed an infiltrating mass in the region of the left maxillary tuberosity behind the last molar tooth and another involving the left mandible at the mandibular foramen and spreading into soft tissues along the attachment of the pterygoid muscles within the left masticator space. The characteristics of these findings on the T1 and T2-weighted images and the enhancement characteristics were interpreted as being consistent with areas of infiltration of MM. The mass along

the mandible is likely related to disease within the marrow space that infiltrated along the mandibular foramen. The patient did not respond favorably to treatment with lenalidomide and carfilzomib. She is now 2 months post-salvage chemotherapy with a very good response and improvement in her numbness but without complete resolution. The long-term plan is to perform a second ASCT (Figures 1 and 2).

Discussion and Literature Review

In Case 1, the patient presented with complete paresthesia and hyperalgesia of the posterior area of the right mandibular side. Although the patient did not complain of symptoms on the left mandibular side, the CT revealed bilateral trabeculation with mixed density more so on the left mandibular side, bilateral osteolysis, and resorption of the mental nerve canal. Symmetrical symptoms of paresthesia and hyperalgesia of the lower lip and chin can occur although almost all cases present unilaterally and thus can serve as a means of diagnosis. In Cases 2 and 3, panoramic radiographs and CT imaging were unable to detect extra medullary myeloma in the jaw, while MRI revealed infiltration of the mandible, consistent with myeloma. A bone marrow biopsy of Case 2 demonstrated relapse of multiple myeloma and subsequent radiographs revealed lesions that were not present before paresthesia symptoms.



Figure 1: Erythematous soft tissue mass occupying the left maxillary tuberosity in patient #3.



Note: MRI revealing invasion of the left posterior maxilla and tuberosity region not picked up on other imaging modalities.

Figure 2: MRI T1 image of patient #3 arrows indicate infiltrating masses in the L maxillary tuberosity and the left mandibular foramen.

Author	Type of study	Age at time of NCS onset (in years)	sex	MM status at time of NCS onset	Diagnostic imaging able to detect extra medullary myeloma lesions	Diagnostic imaging that failed to detect extra medullary myeloma lesions	Subclass of MM
Katz	Case report	71	Female	Diagnosed	CT	n/a	IgA
	Case report	70	Male	Diagnosed	MRI	CT, Panoramic radiograph	IgA
	Case report	68	Female	Diagnosed	Oropharynx MRI	CT, Panoramic radiograph	IgA
Tejani`	Retrospective study	65	Male	Diagnosed	Radiograph	n/a	n/a
	Retrospective study	59	Male	Diagnosed	CT, Orthopantomogra	n/a	n/a
Elias[11]	Case report	70	Male	Undiagnosed	CT, Panoramic radiograph	n/a	IgG
Yoshioka[16]	Case report	79	Female	Undiagnosed	CT	Panoramic radiograph	n/a
Sanchis[3]	Retrospective study	57	Female	Undiagnosed	n/a	n/a	n/a
Sugawara[17]	Case report	62	Female	Undiagnosed	MRI, Panoramic radiograph	Periapical radiograph	IgG
Hogan[10]	Case report	39	Male	Undiagnosed	MRI	n/a	IgA
Ojanguren[18]	Case report	54	Male	Diagnosed	MRI	n/a	n/a
Vincent[20]	Case report	46	Female	Undiagnosed	Panoramic radiograph	n/a	Monoclonal Ig kappa
Kim[15]	Case report	56	Female	Diagnosed	Mandibular MRI	Brain MRI, nuclear bone scintigraphy,	n/a
Mier[19]	Case report	30	Female	Diagnosed	Mandibular MRI, CT	nuclear bone scintigraph	Non-secretory Ig kappa
	Case report	60	Female	Diagnosed	Panoramic radiograph, nuclear	Radiological bone study	IgA
Vieiraleite Seguno[21]	Case report	81	Male	Undiagnosed	CT, Panormaia raigraph, lateral	n/a	n/a
Lambertenghi Definers[22]	Retrospective study	83	Female	Undiagnosed	Radiograph	n/a	IgG
	Retrospective study	59	Male	Undiagnosed	Radiograph, lateral skull tomogram	n/a	IgA
Colella[23]	Case series	44	Male	Undiagnosed	Panoramic radiograph, CT,	n/a	n/a

key: n/a=not performed or not available

Table 1: Summary of cases with patient characteristics.

NCS may be a sign of recurrence of multiple myeloma with resorption of the mental nerve canal. Patients presenting with unilateral paresthesia with or without hyperalgesia should be further evaluated by MRI for diagnosis of NCS. Early detection is vital as mandibular metastasis suggests an unfavorable prognosis [13]. Some authors view it as a harbinger of tumor progression or relapse [14]. A specific mandibular MRI can help delineate the inferior alveolar nerve and mental nerve and is reported to be able to detect malignant infiltration when dental panoramic radiography and computerized tomography fail to do so [15].

In addition to the 3 patients identified in our case series described above, the literature search provided sixteen additional cases, yielding a total of 19 reported cases of NCS in MM patients (Table 1). 10 (or 53%) of the cases included subjects whose onset of NCS was the first manifestation of MM [3,9,10,16-23]. Otherwise, nine patients were already diagnosed with MM [5,6] of which, two (22%) relapsed (Ojanguren and Case 1) and three (33%) were in remission (Miera and Case 3) at time of onset. Using this data, the median age for NCS onset in MM patients is 61 years (range: 30-83) and gender does not appear to be a factor (male/female ratio is 1:1.1).

Interestingly, all three patients in our study had IgA MM. Though the literature search revealed only 6 studies that included antibody lab results, 3 of these NCS patients also had IgA MM. This is significant since the most common Para protein abnormality present in MM patients is IgG [23]. However, it is known that IgA myelomas behave more aggressively and IgA is the dominant immunoglobulin secreted in the GI tract [24,25]. In summary, since NCS is indicative of disease

progression in MM patients, the ability to correctly diagnose a patient with metastatic progression is vital. Additionally, a patient diagnosed with IgA MM may be more likely to develop NCS and should be educated on the likelihood of relapse associated with unilateral paresthesia of the lip or chin.

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