CASE REPORT

Numb chin syndrome as a presenting symptom of diffuse large B-cell lymphoma with secondary myelofibrosis

Arihant Jain,¹ Sweta Rajpal,¹ Man Updesh Singh Sachdeva,¹ Pankaj Malhotra²

¹Department of Clinical Hematology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

²Department of Hematology and Internal Medicine, PGIMER, Chandigarh, India

Correspondence to
Dr Pankaj Malhotra,
hematpgi@gmail.com

Accepted 8 September 2017

SUMMARY

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma that classically presents with rapidly enlarging lymph nodes. We present a 59-year-old man with unusual clinical presentation of numb chin syndrome (NCS) as the first symptom of disease. On evaluation, he was found to have diffuse extranodal skeletal involvement in the form of lytic-sclerotic lesions and minimal lymphadenopathy. Bone marrow biopsy revealed a poorly differentiated tumour with infarction and extensive myelofibrosis. This was subsequently proven to be DLBCL of germinal centre type on immunohistochemical stain. NCS should alarm the clinician to investigate for an advanced underlying malignancy. Extensive myelofibrosis, though described in carcinomas and low grade lymphomas, may also be seen in high grade DLBCL.

BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is the most common Non-Hodgkin lymphoma (NHL).¹ DLBCL has been classified as a broad category in WHO 2016 classification with multiple subtypes and it may have varying presentations depending on the differences in tumour biology and cell of origin.² Common presenting features of DLBCL include rapidly enlarging lymph nodes and frequent B-symptoms. Bone marrow involvement is seen in 11%–27% cases of DLBCL¹ while skeletal involvement is seen in 10.2% cases.³ We present a case of DLBCL who had unusual constellation of clinical presentation, radiological and pathological findings.

CASE PRESENTATION

A 59-year-old man was referred to haematology department with history of numbness of bilateral lower lip, chin and mandibular gums for duration of 2 months. There was no history of dental extraction/procedure or history suggestive of any periodontal disease. One month later, he developed severe generalised bony pains which were not relieved by analgesics. He had a history of significant loss of weight and appetite as well as drenching night sweats. There was history of significant alcohol consumption (40 g/day) for past 8 years and smoking (20 pack-years). On examination, patient had decreased sensation to pain and touch over both sides of chin and lower lips along with hypoaesthesia of lateral aspect of mandibular

gums and mucosa of lower lips. There were no signs of orodental pathology. Notably, liver and spleen were palpable 4 cm and 2 cm below the costal margins, respectively. The cervical lymph nodes were subcentimetric while no axillary or inguinal lymph nodes were palpable. Examination of the remaining central nervous system and peripheral nervous system was normal.

INVESTIGATIONS

Peripheral blood examination revealed anaemia (haemoglobin —9 g/dL), thrombocytopenia ($17 \times 10^9/L$), leucocytosis ($17 \times 10^9/L$) with leucoerythroblastic picture. Biochemical parameters revealed markedly elevated lactate dehydrogenase (LDH) levels (1120 U/L, normal range 150–270 U/L). Positron emission tomography (PET)-CT scan revealed diffuse ¹⁸F-fluorodeoxyglucose (FDG) avid lytic sclerotic lesions in bilateral humeri, mandible, scapulae, ribs, manubrium sterni, multiple cervicodorsal and lumbar vertebrae, pelvis, sacrum and bilateral femurs (figure 1A–C). Subcentimetric cervical lymph nodes and minimally enlarged mediastinal and intra-abdominal lymph nodes (maximum size 1.7 × 2 cm) with hepatosplenomegaly were also noted on PET-CT scan.

Figure 1 Coronal maximum intensity projection PET/CT scan image from baseline shows FDG-avid diffuse skeletal involvement (block arrows), hepatosplenomegaly and subcentimetric lymphadenopathy (A). Midsagittal PET/CT image showing intense FDG avidity in vertebrae, manubrium sterni and liver (B). Axial fused PET/CT images showing FDG avidity in bilateral mandible (arrows) (C). FDG, ¹⁸F-fluorodeoxyglucose; PET-CT, positron emission tomography CT.

To cite: Jain A, Rajpal S, Sachdeva MUS, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-221245

Gadolinium-enhanced MRI of brain did not show any evidence of leptomeningeal seeding and cerebrospinal fluid examination for malignant cells was negative. The presence of severe thrombocytopaenia precluded invasive testing of deep-seated lymph nodes. For further evaluation, he underwent bone marrow aspiration which yielded a dry tap. However, trephine biopsy revealed extensive myelofibrosis (figure 2A) with focal areas of infarction (figure 2B) and few preserved marrow spaces showed sheets of tumour cells (figure 2C). Reticulin stain highlighted grade three myelofibrosis, WHO 2008 (figure 2D). The tumour cells were strongly positive for CD45 (figure 2E), CD20 (focal, figure 2F), CD10 (figure 2G), bcl2 (figure 2H), bcl6 (focal, figure 2I) and negative for cytokeratin, CD34, c-myc and Mum-1. Ki67 stain showed nuclear positivity in 70% tumour cells (figure 2J). Based on immunohistochemical profile, he was diagnosed as germinal centre type DLBCL, stage IV-B-E-S (RIP1 4/5).

TREATMENT

Patient received prephase chemotherapy with rituximab (375 mg/m²), cyclophosphamide (400 mg/m²) and vincristine (1.3 mg/m²). Patient's bony pains, platelet counts and B-symptoms significantly improved with start of therapy. He is planned for interim assessment after four cycles of Rituximab, Cyclophosphamide, Hydroxydaunomycin, Oncovin, Prednisolone (R-CHOP) therapy.

DISCUSSION

The clinical, morphological and genetic heterogeneity of DLBCL is well known. Highlighting the same, this case also had deviation from the usual clinical, radiological and histological presentation. The patient presented with numb chin syndrome (NCS) as the first symptom in chronology.

NCS is a sensory neuropathy characterised by altered sensation and numbness in the distribution of the mental nerve, a terminal branch of the mandibular division of trigeminal nerve. Any dysfunction along the course of trigeminal nerve and its branches (intracranially and/or extracranially) can cause NCS.⁴ Involvement of fibres of mental nerve can lead to impaired

sensation over the skin of chin and mucous membrane of lower lip. As the mental nerve also supplies sensory innervation to the lateral aspect of mandibular gingiva, gingival hypoesthesia is also occasionally reported in patients with NCS⁵ and was seen in our case. The predilection of mental nerves has been postulated to be due to the presence of rich red bone marrow in the inner table of mandible predisposing the bone to frequent haematogenous tumour seeding.⁵

The aetiologies of NCS include local dental causes causing direct injury, infiltration by systemic malignancies or amyloidosis, inflammatory pathologies like systemic vasculitides and infections inflicting the inferior alveolar or mental nerves.⁶ Ever since the first description of NCS by Charles Bell in a case of metastatic breast carcinoma,⁷ this syndrome has been increasingly recognised as a harbinger for serious systemic malignancies. In a retrospective study of 42 consecutive patients with malignancy associated NCS, lymphoproliferative disorders comprised 14% of the patients.⁴ Haematological malignancies that have been associated with NCS include multiple myeloma, acute lymphoblastic leukaemia, acute myeloid leukaemia, Burkitt lymphoma, DLBCL and post-transplant lymphoproliferative disorders. Bilateral involvement is seen in 10% cases of malignancy-associated NCS.⁸ Bilateral as compared with unilateral chin involvement is more commonly associated with haematopoietic malignancies than solid organ malignancies.⁹ This has been previously attributed to higher propensity for central nervous system (CNS) involvement in haematological malignancies.¹⁰ However, bilateral mandibular metastasis with neural infiltration can also lead to bilateral NCS and was the likely aetiology in the present case.

NCS may present simultaneously or follow the diagnosis of a known cancer but frequently precedes the diagnosis as in our case.¹¹ The diagnosis of this syndrome is predominantly clinical although a detailed radiological imaging of the jaw and MRI of brain is recommended to rule out a local or CNS involvement. In the retrospective review of malignancy associated NCS by Lossos *et al*, 50%, 22% and 14% of NCS cases were as a result of mandibular metastasis, leptomeningeal seeding and base-of-skull lesions, respectively.⁴

The median survival following diagnosis of NCS is up to 5 months if NCS is caused by bone metastasis and 12 months if associated with leptomeningeal seeding.⁴ Thus, this seemingly subtle sign should be always be taken as the harbinger of a sinister aggressive malignancy unless proven otherwise. The resolution of symptoms of NCS with therapy can be used as subtle indicator of chemoresponsiveness of the tumour while persistence of symptoms may indicate refractoriness and reappearance may herald a relapse of tumour.¹² In our case, there was partial improvement in numbness following the administration of prephase chemotherapy suggesting chemoresponsiveness of the disease.

Among the cases with secondary myelofibrosis, metastatic carcinoma and lymphomas are the most common neoplastic pathologies. In a retrospective study of 14 cases, incidence of secondary myelofibrosis in cases of lymphomas was found to be 6.6%, among which 3 (21.4%) cases were DLBCL.¹³ In a PubMed search, only five cases of DLBCL with myelofibrosis at the time of diagnosis have been reported.^{13–15} Although Etienne *et al* demonstrated the resolution of myelofibrosis with chemotherapy in cases of lymphoma and reappearance of fibrosis at the time of relapse,¹³ the exact prognostic significance of myelofibrosis in cases of DLBCL at presentation requires further studies.

Lytic sclerotic lesions on a skeletal survey are not the predominant manifestations of DLBCL although they are frequently reported with non-haematopoietic solid organ malignancies like

Figure 2 Bone marrow biopsy showing areas of fibrosis with sinusoidal dilatation and new bone formation (A), focal areas of infarction (B) and area with preserved tumour cells arranged in the form of sheets (C). Reticulin stain to highlight WHO grade 3+ fibrosis (D). The tumour cells are positive for CD45 (E), CD20, focally (F), CD10 (G), bcl-2 (2 hours), bcl-6 (I) immunohistochemical stains. Ki67 highlights nuclear positivity in around 70% tumour cells (2J inset).

prostate and breast. The prevalence of primary bone lymphoma (PBL) is only up to 2% in cases of DLBCL, and bones are secondarily involved in up to 10% of patients in patients with DLBCL, mostly in association with bulky nodal and extranodal disease at other sites.^{1 16}

The definition of PBL varies throughout the literature. Generally, this entity is defined as malignant lymphoma arising within the medullary cavity of a single bone without concurrent regional lymph node or visceral involvement.¹⁷ In contrast, Shoji and Miller permitted lymph node metastases but stipulated that the interval between the onset of symptoms of the primary focus and the appearance of distant metastases should be greater than 6 months.¹⁸ The presence of diffuse skeletal involvement and morphology of sheets of poorly differentiated cells initially led us to suspect a diagnosis of metastatic carcinoma, however, immunohistochemistry helped us in clinching the appropriate diagnosis of Germinal Center B cell (GCB)–DLBCL.

The pattern of presentation in our patient supports the possibility that lymphoma had primarily arisen in the skeleton and lymph nodes were secondarily involved. We reiterate the fact that in cases with diffuse skeletal involvement by metastatic malignancy on radiology and poorly differentiated histomorphology on biopsy, the presence of subcentimetric lymph nodes and/or hepatosplenomegaly should be taken as soft clinical pointers towards the possibility of a lymphoma which can be resolved with relevant immunohistochemistry.

Learning points

- Numb chin syndrome should be considered as an ominous sign of an underlying advanced malignancy and thoroughly investigated with radiological and histological studies.
- Although a diffuse skeletal involvement with poorly differentiated morphology and extensive myelofibrosis may masquerade metastatic carcinoma, however, it may be a presenting feature of aggressive diffuse large B-cell lymphoma.

Contributors AJ: senior resident who has seen the patient in outpatient department and was involved in writing the manuscript. SR: senior resident who was involved in making diagnosis of diffuse large B-cell lymphoma in pathology and writing of manuscript. MUSS was involved in making diagnosis of diffuse large B-cell lymphoma and correction of manuscript. PM was the treating physician of this patient and corrected the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Campo E, Swerdlow SH, Harris NL, *et al.* The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood* 2011;117:5019–32.
- 2 Swerdlow SH, Campo E, Pileri SA, *et al.* The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;127:2375–90.
- 3 Lehnert N, Krämer I, Saadati M, *et al.* Analysis of prognostic factors in patients with newly diagnosed diffuse large B-cell lymphoma and skeletal involvement. *BMC Cancer* 2017;17:128.
- 4 Lossos A, Siegel T. Numb chin syndrome in cancer patients: etiology, response to treatment, and prognostic significance. *Neurology* 1992;42:1181–4.
- 5 Soares EC, Costa FW, Rocha-Filho FD, *et al.* Metastatic prostate adenocarcinoma associated with numb chin syndrome. *J Craniofac Surg* 2011;22:2366–8.
- 6 Divya KS, Moran NA, Atkin PA. Numb chin syndrome: a case series and discussion. *Br Dent J* 2010;208:157–60.
- 7 Furukawa T. Charles Bell's description of numb chin syndrome. *Neurology* 1988;38:331.
- 8 Lata J, Kumar P. Numb chin syndrome: a case report and review of the literature. *Indian J Dent Res* 2010;21:135–7.
- 9 Sozaki M, Yamazaki H, Aoki T, *et al.* Bilateral numb chin syndrome leading to a diagnosis of burkitt's cell acute lymphocytic leukemia: a case report and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011;111:e11–e16.
- 10 Algahtani H, Shirah B, Bassuni W, *et al.* Bilateral numb chin syndrome as the initial presentation of Burkitt's lymphoma/leukemia: a report of two cases and review of the literature. *Case Rep Hematol* 2016;2016:3791045.
- 11 Elahi F, Luke W, Elahi F. Intractable facial pain and numb chin due to metastatic esophageal adenocarcinoma. *Case Rep Oncol* 2014;7:828–32.
- 12 Barrett AP. Selective anesthetics of the inferior alveolar nerve in leukemia and lymphoma. *J Oral Maxillofac Surg* 1985;43:992–4.
- 13 Etienne A, Gruson B, Chatelain D, *et al.* Myelofibrosis-associated lymphoproliferative disease: retrospective study of 16 cases and literature review. *Adv Hematol* 2009;2009:1–5.
- 14 Kumagai T, Satoh Y, Koshiishi M, *et al.* 18F-FDG-PET/CT is effective in distinguishing myelofibrosis due to bone marrow infiltration of diffuse large B-cell lymphoma from triple-negative primary myelofibrosis. *Rinsho Ketsueki* 2017;58:228–32.
- 15 Meckenstock G, Wehmeier A, Schaefer HE, *et al.* Lymphoid myelofibrosis associated with high grade B cell lymphoma of the liver: morphological, cytogenetic, and clinical features. *Leuk Lymphoma* 1997;26:197–204.
- 16 Castillo JJ, Winer ES, Olszewski AJ. Sites of extranodal involvement are prognostic in patients with diffuse large B-cell lymphoma in the rituximab era: an analysis of the surveillance, epidemiology and end results database. *Am J Hematol* 2014;89:310–4.
- 17 Coley BL, Higinbotham NL, Groesbeck HP. Primary reticulum-cell sarcoma of bone; summary of 37 cases. *Radiology* 1950;55:641–58.
- 18 Shoji H, Miller TR. Primary reticulum cell sarcoma of bone. *Significance of clinical features upon the prognosis Cancer* 1971;28:1234.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow