Clinical Reasoning: A pregnant woman with chin numbness

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Section 1

A 36-year-old 24 weeks pregnant woman (G1P0) presented to the emergency department with a 5-day history of paresthesias involving the left side of her chin beginning at the midline and extending towards the corner of her mouth as well as intermittent bilateral upper extremity paresthesias. There were no accompanying weakness, bulbar symptoms, or bowel or bladder difficulties, and no recent history of trauma to the head or neck. She had a 2-day history of night sweats. Aside from these recent symptoms, she had been well. Her medical history was notable for hypothyroidism, for which she was taking levothyroxine 125 μg daily, and septic arthritis of the right hip 2 years prior. The emergency medicine physician examined her and no focal deficits were noted. She declined further investigations and went home.

One week later, she returned with persistent drenching night sweats, severe fatigue, and bilateral chin numbness. In addition, her arm paresthesias had evolved to lancinating pain described as "electrical" and left arm weakness. She was examined by an emergency medicine physician, who noted bilateral pinprick sensation loss on her chin from the midline to the corners of her mouth. Cranial nerves were otherwise normal. Motor examination demonstrated normal bulk and tone. Grade 4+/5 weakness of the left deltoid, biceps, and wrist extensors was noted. Reflexes and sensory examination were normal. The neurology service was consulted.

Questions for consideration:

1. How would you localize the patient's symptoms?
2. What is your differential diagnosis?

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Section 2

Chin paresthesias localize to the trigeminal nerve's mandibular segment, and potentially its distal branch, the mental nerve. The trigeminal nerve exits the pons to form its ganglion in Meckel cave, and has 3 principal branches: ophthalmic, maxillary, and mandibular. The mandibular branch passes through the foramen ovale and divides into anterior and posterior trunks. The anterior trunk innervates the buccal mucosa and the masticatory muscles. The posterior trunk divides into the auriculotemporal, lingual, and inferior alveolar nerves, and it is the inferior alveolar nerve that courses through the mandible and exits via the mental foramen to become the mental nerve. The paired mental nerves then supply sensation to the teeth in the lower jaw, lateral gums, lower lip, and chin (figure 1).

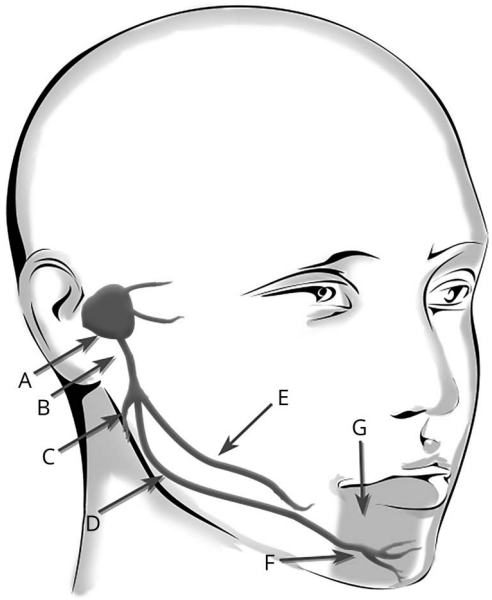
The bilateral upper extremity paresthesias are more challenging to precisely localize; however, they are most likely in keeping with a lesion in the cervical cord or its exiting nerve roots. The patient has radicular-type pain, and with left arm weakness in the absence of upper motor neuron findings, but spanning multiple peripheral nerve territories, a cervical polyradiculopathy would be the favored localization.

There could be multiple lesions involving bilateral mandibular segments of the trigeminal nerve as well as the cervical nerve roots, but a more parsimonious explanation would be a leptomeningeal process encircling the brainstem and cervical cord.

Proceeding with the hypothesis of leptomeningeal disease, the differential diagnosis is broad, and would include infections such as HIV and tuberculosis, inflammatory etiologies such as sarcoidosis and Sjögren syndrome, and neoplastic infiltration.[1] There is a history of new-onset drenching night sweats, which is particularly concerning for a malignancy. Malignancies in pregnancy overall are rare, with the most common being breast, cervical, melanoma, Hodgkin lymphoma, and leukemia.[2]

The presence of a numb chin is a critically important clinical clue. Patients without an identified traumatic cause or local infection should be investigated for a malignancy.[3] Numb chin syndrome (NCS) has been reported over the last 50 years as a highly specific presentation for leptomeningeal carcinomatosis, mandibular or skull base metastases, or perineural tumor infiltration involving the trigeminal nerve complex.[1] A systematic review of 136 cases found NCS to be the first manifestation of cancer in 27.7% and the first symptom of recurrence in 37.7%.[3] Many different causative malignancies have been reported, but in that systematic review, 40.4% of patients had breast cancer, 20.5% lymphoma, 6.6% prostate cancer, and 5.1% leukemia.[3]

Figure 1 Anatomy of the mental nerve and associated area of numbness



From the gasserian ganglion (A), the mandibular nerve (B) exits the skull via the foramen ovale. The posterior trunk divides, giving rise to the auriculotemporal (C), inferior alveolar (D), and lingual (E) nerves. The inferior alveolar nerve travels in the mandible, entering through the mandibular canal. It then gives rise to the mental nerve (F), which exits through the mental foramen. The shadowed area (G) corresponds to the sensory region of the mental nerve and is the classically affected area in numb chin syndrome. Figure courtesy of Lucas Roberts.

Question for consideration:

1. How would you proceed with investigations?

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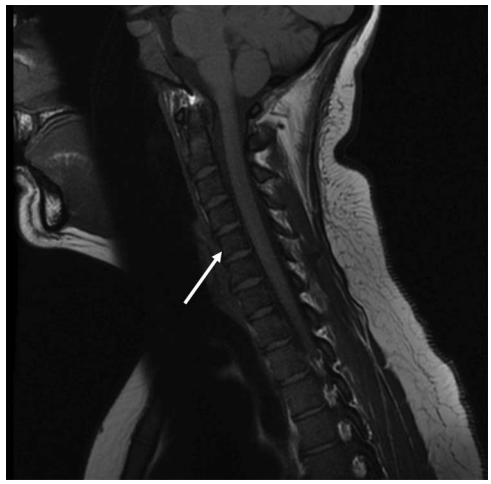
Section 3

As neoplastic infiltration of the leptomeninges is the leading diagnosis after the history and physical examination, a thorough laboratory work-up and imaging studies are needed. A complete blood count demonstrated mild anemia (11.2 g/dL), low platelets (78×10^3/μL), and elevated white blood cells (WBC) (17.9×10^3/μL). Differential showed 13,000/μL neutrophils, 600/μL metamyelocytes, and 1,300/μL myelocytes. While an elevated WBC count with predominantly neutrophils often suggests an acute infection, the presence of very immature cell types (myelocytes), as well as the anemia and thrombocytopenia, is concerning for acute leukemia. Additional systemic laboratory work-up demonstrated normal electrolytes, creatinine, creatine kinase, liver panel, thyroid-stimulating hormone, free T3 and T4, iron, and total iron binding capacity, but markedly elevated lactate dehydrogenase (1,532 U/L), ferritin (545 ng/mL), and C-reactive protein (64 mg/L). Blood and urine cultures were negative.

A lumbar puncture is needed to rule out a central nervous infection and abnormal cytology would support leptomeningeal carcinomatosis, but obtaining neuroimaging of the brain and cervical spine first would be prudent. According to recent American College of Gynecology guidelines, gadolinium should be avoided in pregnancy, and MRI sensitivity will thus be reduced.[4] Contrast-enhanced CT is an option in this patient, especially as she is beyond the first trimester, but it is not the ideal imaging modality for brainstem and spinal cord soft tissue pathology.[4]

An MRI of the brain and cervical spine showed no intrinsic brain or spinal cord abnormality, and the absence of gadolinium precluded a detailed examination of the leptomeninges. The vertebral bone marrow, however, was abnormal with diffuse T1 hypointensity (figure 2). In the context of the patient's clinical presentation, the finding is suggestive of neoplastic marrow infiltration. A lumbar puncture subsequently showed normal cell count, differential, glucose, and protein. Cytology demonstrated rare lymphocytes and monocytes, but no atypical cells. A single lumbar puncture for cytology has a sensitivity of less than 50%.[5] The literature suggests factors that improve yield include obtaining greater than 10.5 mL of CSF, processing the specimen immediately, performing 2 or more taps, and having nearby clinical or radiologic disease.[5]

Figure 2 T1 sagittal MRI of the cervical spine reveals diffuse hypointensity of the bone marrow (arrow) in keeping with cellular infiltration from acute leukemia



Questions for consideration:

1. You have neurologic findings, no causative lesion on imaging, and a concerning but inconclusive systemic workup for a hematologic malignancy. What are your next steps?
2. How does the patient's pregnancy change your management?

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Section 4

At this point, the case is extending beyond neurology, and it is imperative to obtain guidance from other specialties. Hematology arranged an urgent bone marrow biopsy. While a second lumbar puncture may have shown atypical cells, a bone marrow biopsy is definitive. It demonstrated acute myeloid leukemia (AML), myoblastic subtype, necessitating urgent chemotherapy.

Obstetrics, concerned that they may need to deliver the baby at just 25 weeks, administered betamethasone in order to encourage fetal lung development.[6] Even with modern neonatal intensive care, such a severely premature infant is likely to experience significant morbidity.[6] Interestingly, the steroids improved the patient's radicular pain significantly, potentially by reducing the extent of the neoplastic leptomeningeal deposits.

The hematologist and neonatologist had a detailed conversation with the patient and her husband. Starting treatment with idarubicin and cytarabine during pregnancy and incurring potential risks to the fetus from treatment was balanced against the risks of severe prematurity from immediate delivery. These include more frequent hospital admissions, greater burden of chronic disease, and overall poorer general health.[7] In a systematic review of 87 pregnant patients with AML treated with systemic chemotherapy, 50% of those exposed in the first trimester had poor fetal outcomes, and some of those exposed later still experienced intrauterine fetal death, growth restriction, premature delivery, and various congenital abnormalities.[8] Additional risks discussed with the patient included hemorrhage from spontaneous premature labor with treatment-induced thrombocytopenia and opportunistic infections from immunosuppression. After careful consideration, the patient elected to undergo induction chemotherapy while continuing her pregnancy. She completed it without complications, and a follow-up bone marrow biopsy showed remission of AML; however, consolidation chemotherapy was still needed.

The hematologist and obstetrician discussed with the patient the risks of continuing with pregnancy during consolidation chemotherapy vs preterm delivery. At this stage, the fetus was nearing 32 weeks, transitioning from very preterm (<32 weeks) with the greatest potential for morbidity and mortality to moderate preterm (32–33 weeks) when outcomes are improved, but not yet equivalent to term.[7] The patient delivered a healthy baby at 32 weeks by caesarean section and consolidation chemotherapy was initiated. She eventually underwent allogenic unrelated donor hematopoietic stem cell transplant. Her upper extremity pain, weakness, and sensory symptoms resolved, and at last follow-up, she had mild residual numbness of the left side of her chin.

Discussion

This is a complex case with a few critical take-home messages. A numb chin must always alert the clinician to thoroughly investigate for an underlying malignancy. Obtaining enhanced imaging, as long as it is permitted by the clinical situation, of the brain, skull base, and mandible is required to fully evaluate the trigeminal nerve complex.[9] A detailed systemic workup looking for cancer should be tailored to the clinical history and examination. As a neurologist, it is crucial to recognize NCS and to facilitate the diagnosis of cancer, but it is just as important to involve the correct specialists in order to provide comprehensive patient care. The treatment of NCS depends on its etiology, and in those cases caused by neoplasms, the specific oncologic management is dependent on the tumor's origin, as well as the patient's clinical status. As demonstrated, pregnancy may further complicate management. Additional considerations include risks to the fetus from treatment of the malignancy and determining the safest timing of delivery, which re-emphasize the importance of consultation with other specialists. Retrospective data exist to inform treatment decisions for leukemia in pregnancy, but in the case of numb chin syndrome in pregnancy, there is a paucity of evidence in the literature.

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Appendix Authors

Name	Location	Role	Contribution
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Gabriela S. Gilmour, MD	University of Calgary, Canada	Author	Editing and critical revisions to the intellectual content, figure creation.
Marcus W. Koch, MD, PhD	University of Calgary, Canada	Author	Editing and critical revisions to the intellectual content

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