Metastatic Signet Ring Cell Gastric Carcinoma Bypassing Virchow's Node: An Unexpected Etiology of a Painful Neck Mass.

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Running title: Signet Ring Cell Gastric Carcinoma Neck Metastasis



ABSTRACT: Metastatic head and neck masses usually result from locoregional spread of mucosal squamous cell carcinoma. We report metastatic signet ring cell gastric carcinoma presenting as a painful Level V neck mass without Virchow node; carcinomatous spread spared supraclavicular nodes at the junction of the thoracic duct and left subclavian vein.

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KEYWORDS: Neck mass, neck pain, lymph node, Virchow's lymph node, gastric cancer, gastric carcinoma; head and neck cancer, metastasis, metastatic, differential diagnosis; locoregional spread; Troisier's sign; signet ring cell carcinoma; SRCC; radiological imaging, computed tomography, CT, PET, MRI.

KEY CLINICAL MESSAGE: Metastatic lymph nodes of the head and neck are often associated with locoregional spread of mucosal squamous carcinoma but in rare instances visceral malignancies, may bypass Virchow's node. The possibility of distant metastasis should be considered.

INTRODUCTION

Although clinical practice guidelines have helped standardize evaluation and management of neck masses [1], the differential diagnosis of lateral neck masses is vast, encompassing inflammatory, congenital, and neoplastic etiologies [2]. Presence of a painful, fixed neck mass in an adult patient should rouse suspicion of malignancy. While lymphatic spread of head and neck mucosal squamous cell carcinoma is common, fixed neck masses may arise from myriad etiologies, including distant spread of a visceral malignancy [3]. Infraclavicular primary carcinomas that metastasize to the head and neck usually do so via lymphatics, classically manifesting an enlarge left-sided supraclavicular lymph node, or Virchow's lymph node (VN). Muscle metastasis via hematogenous spread has also been reported but is a far rarer event [4,5]. We report signet ring cell gastric adenocarcinoma that bypassed Virchow's node, presenting as a painful mass of the left posterolateral neck.

CASE PRESENTATION

A 78-year-old white woman presented with a 6-month history of progressive left neck swelling and recent onset of left neck pain with lateral movement. He medical history was also notable for a history of clear cell renal cell carcinoma that was removed in May 2014 and without recurrence. Otherwise, she was in good health with negative history. She reported being a former smoker with successful tobacco cessation 15 years prior and she consumed no alcohol. She adhered to a Mediterranean diet, was appropriately nourished, and consumed 2 liters of water daily. She denied symptoms of poor appetite, weight loss, early satiety, dysarthria, dysphagia, or other head and neck or gastrointestinal symptoms. Her clinical examination showed a firm, hypomobile mass involving Level V of neck, with absence of nodal enlargement in the supraclavicular fossa or any other regions of the head and neck. Flexible endoscopy revealed no lesions in the mucosa of the upper aerodigestive tract, and an

ultrasound-guided biopsy of the left neck mass was non-diagnostic.

Because of patient's known cancer history, comprehensive imaging evaluation was then performed, including magnetic resonance imaging (MRI) with gadolinium, neck and thorax contrast computed tomography (CT), and total body positron emission tomography (PET) CT. Head and neck MRI (**Figure 1 A, B**) and CT (**Figure 1 C, D**) imaging identified an enhancing posterolateral neck lesion measuring 37 x 35 x 15 mm. The mass was adjacent to and invading the sternocleidomastoid muscle. Thoracic CT-scan demonstrated no pathological masses or enlarged lymph nodes. Repeat ultrasound guided fine needle biopsies were again non-diagnostic. The woman requested surgical removal of the neck mass, and she was therefore taken to the operating theatre for rigid endoscopy of the upper respiratory tract and excisional biopsy of the left neck mass. Endoscopy revealed no abnormalities. Through a small neck incision, the neck mass was resected "in bloc", also excising a small cuff of surrounding fibro-adipose tissue and sternocleidomastoid musculature.

Frozen section pathology demonstrated cellular atypia consistent with gastric carcinoma (**Figure 2 A**, **B**, **and C**). After obtaining consent from family, esophagogastroduodenoscopy with biopsy was performed with the patient under general anesthesia. This evaluation identified a gastric ulcer situated on the greater curvature of the stomach and the anterior wall of pre-pyloric region. Serial biopsies were performed of the primary lesion and the adjacent tissues. Final histopathology demonstrated HER2 negative signet-ring cell carcinoma. Following multidisciplinary review, the patient started chemotherapy with folinic acid, 5-fluorouracil (5-FU), and foxaliplatin (FOLFOX) without a response. The treatment regimen was transitioned to folinic acid (leucovorin), 5-FU, and irinotecan (FOLFIRI). The patient experienced tumor regression and remission; as of most recent follow-up in August 2020, the patient was without evidence of disease.

DISCUSSION

Thorough evaluation for neck masses is critical, and rarely distant primary tumors may present with metastasis to the head and neck [4]. Our patient had no clinical signs of visceral disease [4]; she denied gastric pain, decreased appetite, or weight loss [6]. Gastric carcinoma is insidious, with the epidemiological data showing that 80% of patients with gastric cancer have metastases at time of diagnosis [7]. This metastatic gastric carcinoma was highly unusual in sparing the supraclavicular nodal basin. Because visceral malignancies are often initially asymptomatic at the primary site, biopsy of suspect lymph nodes may facilitate diagnosis [8]. While metastasis of gastric cancer to the head and neck is uncommon [5], Virchow's node (Troisier's sign) is well-recognized [3].

Virchow's node in visceral malignancy results from tumor metastasis through the thoracic duct, and it is extremely rare for gastric carcinoma to bypass this lymph node basin [9,10]. Virchow nodes may compress or invade adjacent neurovascular structures, causing thoracic outlet syndrome, brachial plexopathy, phrenic neuropathy, or Horner's syndrome. Many sources of malignancy – gastrointestinal, hepatobiliary, ovarian, testicular, renal, and other origins – may present with a Virchow's node, underscoring its importance across a broad range of medical and surgical specialties. Level V lymph node metastasis by gastric carcinoma without an associated Virchow's node is extremely rare [10]; in fact, only one other case has been previously reported in literature [11]. This unusual case highlights enduring principles, including vigilance about the possibility of a distant primary tumor, while ensuring diligent surveillance for upper aerodigestive tract lesions.

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AUTHORS' CONTRIBUTION: ADS, LdA, MB: study design and article writing; GL, PG, MP and TT collection of clinical data; GR and MM literature review, criticism and review of paper.

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REFERENCES

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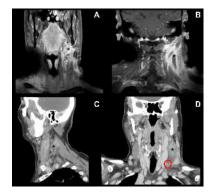
- Pynnonen MA, Gillespie MB, Roman B, et al. Clinical Practice Guideline: Evaluation of the Neck Mass in Adults. Otolaryngol Head Neck Surg. 2017;157: S1-S30.
- 2. Haynes J, Arnold KR, Aguirre-Oskins C et al. Evaluation of neck masses in adults. Am Fam Physician. 2015; 91:698-706.
- Aghedo BO, Kasi A. Virchow Node. SourceStatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.
- 4. Aguirre LE, Salcedo J, Zuquello R et al. Metastatic involvement of skeletal muscle from gastric adenocarcinoma. Oxf Med Case Reports. 2019; 2019: omz081.
- 5. Goto S, Takeda H, Sasahara Y et al. Metastasis of advanced gastric cancer to the extraocular muscle: a case report. J Med Case Rep. 2019; 13:107.
- Sundriyal D, Kumar N, Dubey SK et al. Virchow's node. BMJ Case Rep. 2013; pii: bcr2013200749.
- Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol Biomarkers Prev.* 2014;23(5):700-713. doi: 10.1158/1055-9965.EPI-13-1057
- 8. Suh YS, Yang HK. Screening and Early Detection of Gastric Cancer: East Versus West. *Surg Clin North Am.* 2015;95(5):1053-1066. doi: 10.1016/j.suc.2015.05.012
- Zdilla MJ, Aldawood AM, Plata A, Vos JA, Lambert HW. Troisier sign and Virchow node: the anatomy and pathology of pulmonary adenocarcinoma metastasis to a supraclavicular lymph node. *Autops Case Rep.* 2019;9(1): e2018053. Published 2019 Feb 25. doi:10.4322/acr.2018.053.
- López F, Rodrigo JP, Silver CE, et al. Cervical lymph node metastases from remote primary tumor sites. *Head Neck*. 2016;38 Suppl 1(Suppl 1):E2374-E2385. doi:10.1002/hed.24344
- 11. Takashima T, Nakata B, Hatama M, et al. Gastric cancer with cervical lymph node metastasis as the first presentation: report of a case. Int Surg. 2008; 93:295–299.



FIGURE LEGENDS

Figure 1: **A**, **B**) MRI showing a metastatic lesion of the neck with histology from the primary lesion. Coronal contrast-enhanced T1-weighted MRI slices show the enhancing lesion of the left posterolateral neck (asterisks). The lesion's location, encroaching on sternocleidomastoid musculature and prevertebral fascia, correlates with clinical symptoms of neck pain with lateral movement. **C**, **D**) Parasagittal and coronal sections on CT scan confirmed the mass (asterisk) and infiltration of surrounding structures. The round circle denotes a normal lymph node.

Figure 2: Histology 200x magnification. A) Incisional biopsies of the left sternocleidomastoid muscle and superficial cervical fascia. Hematoxylin-eosin staining shows histological features consistent with gastric carcinoma (G2). B) Immunohistochemistry with CKAE1/AE3 shows positive nuclear staining indicative of carcinoma. C) Eosin and hematoxylin staining of gastric tissue from endoscopy demonstrates classic histopathology for signet-ring cell carcinoma, including signet-ring cell vacuoles (black arrow).



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