Isolated synchronous Virchow lymph node metastasis of sigmoid cancer: A case report

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Abstract

BACKGROUND
Colorectal cancer (CRC) is one of the most common malignant tumors of the digestive tract. Lymphatic metastases of this tumor are mostly confined to the
CASE SUMMARY
In this report, we describe a patient with sigmoid carcinoma and isolated synchronous supravacular lymph node metastases. A 56-year-old male presented with a left cervical mass that was confirmed as a lymph node metastasis from sigmoid cancer by several auxiliary examinations. After 6 cycles of chemotherapy with the 5-fluorouracil, leucovorin and oxaliplatin + cetuximab regimen, the sigmoid colon tumor and Virchow’s lymph node metastasis were significantly smaller than before treatment, and no new metastatic sites were observed. Considering the effects of chemotherapy on quality of life, resection of the primary tumor was performed followed by 4 cycles of chemotherapy with the original chemotherapy regimen. Virchow’s lymph node dissection was selected by mutual consultation between the patient and us. After the second surgery, the patient received capecitabine and cetuximab chemotherapy and did not experience recurrence or metastasis during follow-up.

CONCLUSION
In conclusion, supravacular lymph node metastasis without any other solid organ metastasis is a potential metastatic pathway for CRC. In addition, after resection of the primary lesion, postoperative chemotherapy combined with supravacular lymph node dissection is feasible for the treatment of patients with CRC and isolated synchronous Virchow’s lymph node metastases.

Key Words: Virchow’s lymph node; Metastasis; Colorectal cancer; Case report

INTRODUCTION
Colorectal cancer (CRC) is one of the most common malignant tumors of the digestive tract[1]. CRC frequently metastasizes to the regional lymph nodes, liver, lung, and peritoneum[2]. CRC with distant lymph node site metastasis is rare, and synchronous distant lymph node metastasis from CRC without any other solid organ metastasis is extremely rare. Therefore, we report the case of a patient with sigmoid colon cancer who presented with isolated synchronous Virchow’s lymph node metastasis.
CASE PRESENTATION

Chief complaints
A 56-year-old male presented with a left cervical mass that had been present for one month.

History of present illness
The patient's left cervical mass was incidentally discovered and no other clinical manifestations.

History of past illness
The patient was previously diagnosed with diabetes and took oral hypoglycemic drugs for control of blood glucose level.

Personal and family history
The patient lived in Jining, China. He did not smoke and was not addicted to alcohol. No relevant family history was reported.

Physical examination
Physical examination revealed a solid small peanut-sized mass in the left supraclavicular region.

Laboratory examinations
The laboratory assessment revealed that carcinoembryonic antigen (CEA), CA199, and CA724 serum levels were moderately elevated.

Imaging examinations
Ultrasoundography of the cervical mass showed that multiple hypoechoic masses were present in the left supraclavicular fossa, and the larger mass measuring 0.9 cm × 0.5 cm had a clear border and unclear internal structure. This mass was mildly enhanced on contrast-enhanced computed tomography (CT). Positron emission tomography/CT (PET/CT) scan demonstrated that no significant fluorodeoxyglucose (FDG) uptake was observed in the left supraclavicular region. To determine the nature of the enlarged lymph nodes, lymph node biopsy was performed, and histopathological examination revealed metastatic adenocarcinoma. In the immunohistochemical analysis, the biopsied tissue was positive for SP-B, CK8/18, CK20, CDX-2 and P504S expression with a Ki-67 index of 80%; the tissue was negative for CK5/6, CgA, P40, P63, CK7, TTF-1, Napsin A, SPA and Syn expression. The laboratory assessment revealed that CEA, CA199, and CA724 serum levels were moderately elevated. In addition, high-throughput gene sequencing showed wild type K-Ras.

FINAL DIAGNOSIS
According to the results of the auxiliary examination, this patient was diagnosed with late-stage sigmoid colon cancer with distant lymph node metastasis.

TREATMENT
The patient received chemotherapy with the 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) + cetuximab regimen. After 6 cycles of chemotherapy, the patient was reexamined with CT and ultrasonography, and the results showed that the sigmoid colon tumor and Virchow’s lymph node were significantly smaller than before treatment and no new metastatic sites were found. Considering the effects of chemotherapy on quality of life, the patient and his family members strongly
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Figure 1 Contrast-enhanced computed tomography: The mass appeared to be mild enhancement. A: Axial view; B: Coronal view.

Figure 2 Positron emission tomography-computed tomography: No significant fluorodeoxyglucose uptake was observed in left supraclavicular region.

requested surgery after receiving education on the risks and benefits of surgery and other therapeutic regimens. Therefore, sigmoid carcinoma resection and mesenteric lymph node dissection were performed. Histological examination (Figure 6) showed moderately differentiated adenocarcinoma localized in the mucosa, and one of five paracolic lymph nodes contained metastatic carcinoma (pT1N1M1). Immunohistochemically, the excised tissues were positive for CK20, MSH2 and SATB2 and negative for CK7 (Figure 7). After surgery, the patient received the same chemotherapy regimen as before. After undergoing 4 cycles of chemotherapy, Virchow’s lymph node dissection was selected by mutual consultation between the patient and us. We removed the lymph nodes in the triangle bounded by the lower abdomen of the omohyoid, the posterior margin of the sternocleidomastoid and the superior clavicle (the level IV and VB lymph nodes of the neck). Histological examination revealed that five of the eight dissected cervical lymph nodes contained metastatic carcinoma. Immunohistochemically, these lymph nodes were positive for CDX2, SATB2, CK20, KIAA1429 and RBM15 and negative for IC3H13, CK7, TTF1 and P40. Histopathologic examination and immunohistochemistry staining again confirmed sigmoid metastasis. During the dissection of the enlarged left supravacular lymph node, there was clear fluid outflow from the left venous angle, which suggested lymphatic leakage. We
Figure 3 The left supraclavicular lymph node biopsy exhibited typical morphological findings of adenocarcinoma (hematoxylin & eosin staining × 200).

Figure 4 Colonoscopy examination: A pedunculated polyp measuring 2.0 cm in diameter was observed in sigmoid colon.

Figure 5 Pathological finding of the endoscopic biopsy (hematoxylin & eosin staining × 100): Carcinoma tissue invades the muscularis mucosa.

immediately sutured the site with silk thread and pressed it with a gelatin sponge; subsequently, the fluid outflow stopped. On the second day after surgery, the left cervical drainage tube drained approximately 2000 mL milky white fluid. After the diagnosis of postoperative lymphatic leakage, the patient was treated with diet restriction, total parenteral nutrition, local wound compression, and somatostatin pumping. From the 4th to 7th day after surgery, approximately 500-100 mL of clear liquid was drained from the left cervical drainage tube per day. On the 10th day after surgery, 2 mL Pseudomonas aeruginosa (1.8 × 10^9/mL, Beijing Wanteer Biopharmaceutical Co. Ltd) was injected near the left venous corner under the guidance of ultrasonography, and the drainage tube was clamped. Thirty minutes after the injection, the patient developed chills and high fever, with the highest body temperature recorded at 39 ℃. After a large amount of fluid infusion, anti-inflammatory and other symptomatic treatments, the patient's symptoms gradually improved, and no further lymphatic fluid drainage was observed. Considering the patient has reached the predetermined number of cycles of chemotherapy after sigmoid tumor resection, the patient received a maintenance chemotherapy regimen with capecitabine and cetuximab after the second surgery.
OUTCOME AND FOLLOW-UP
At half of a year after the surgery, the patient was asymptomatic, and there were no signs of tumor recurrence or progression.

DISCUSSION
CRC can spread by lymphatic, hematogenous, and transperitoneal dissemination as well as direct extension. Regional lymph nodes (52%), liver (78%), lung (20%), and peritoneum (29%) are frequently observed metastatic sites of CRC[2]. CRC with distant lymph node metastasis is very rare. Although a few cases[3-6] of synchronous supraclavicular lymph node metastases from colorectal carcinoma have been reported (Table 1), most were complicated with multiple metastases or treated exclusively with chemotherapy. To the best of our knowledge, this is the first case of lymph node
Table 1 Long-term survival of cases with synchronous Virchow lymph node metastasis of colorectal cancer

| No. | Ref.          | Year | Age/gender | Primary location | Metastasis of another organ | Resection of Virchow LN | Postoperative chemotherapy | Disease free survival time | Overall survival time |
|-----|---------------|------|------------|------------------|-----------------------------|-------------------------|---------------------------|----------------------------|-----------------------|
| 1   | Watanabe et al[3] | 2009 | 73/Male    | Cecum            | Paraaortic lymph nodes; Lung | -                       | 5-fluorouracil, Leucovorin, FOLFOX, FOLFIRI | -                          | 3 yr                  |
| 2   | Hirose et al  [4]   | 2010 | 57/Male    | Rectum           | -                            | -                       | FOLFOX, FOLFIRI            | -                          | 3 yr                  |
| 3   | Ando et al  [5]    | 2013 | 63/Male    | Sigmoid colon    | -                            | -                       | FOLFOX, FOLFIRI            | -                          | 5 yr                  |
| 4   | Suliman et al  [6] | 2019 | 54/Male    | Transverse colon | -                            | +                       | FOLFOX, FOLFIRI            | -                          | -                     |
| 5   | Our case         | 2020 | 56/Male    | Sigmoid colon    | -                            | +                       | FOLFOX, capecitabine, cetuximab | So far                    | So far                |

FOLFOX: Fluorouracil, leucovorin and oxaliplatin; FOLFIRI: Fluorouracil, leucovorin and irinotecan; LN: Lymph node.

surgical indications for colorectal tumors with distant lymph node metastases remain controversial[9]. Traditionally, supraclavicular lymph node metastasis is considered a relative contraindication to surgery. CRC with supraclavicular lymph node metastasis is typically diagnosed as stage IV and indicates poor prognosis[10-12]. However, some CRC patients with supraclavicular lymph node metastasis achieve a good response and better prognosis after chemotherapy[3-6]. Therefore, preoperative chemotherapy combined with surgical resection has been reconsidered for this indication given the development of increasingly effective chemotherapy regimens [13]. In our case, because genetic sequencing of the patient's sigmoid tumor revealed at wild type K-Ras gene, the patient was administered six cycles of chemotherapy with the FOLFOX + cetuximab regimen. Due to the timely intervention with an appropriate systemic chemotherapy regimen, the patient did not develop systemic organ metastasis, and the primary tumor and metastatic lymph nodes showed a good response. This notion was further confirmed by postoperative pathology showing a retraction of sigmoid tumor invasion and fewer paracolic lymph node metastases. After resection of the primary site and 4 cycles of postoperative chemotherapy with the original regimen, this patient underwent left supraclavicular region lymph node dissection followed by chemotherapy with capecitabine + cetuximab. During the follow-up period, no signs of tumor recurrence or progression were observed. Therefore, we suggest that preoperative chemotherapy combined with surgical resection may be used to extend the survival interval of patients with CRC, especially patients who respond well to chemotherapy and have a strong desire to undergo surgery.

Previous literature has reported that PET/CT offers value in predicting distant tumor metastases[14]. In our case, however, no significant FDG uptake was observed in the patients' left supraclavicular lymph nodes on PET/CT. The false negative PET/CT results of this patient may be related to the smaller diameter of the supraclavicular lymph nodes. The standard uptake value (SUV) of the lesion is generally proportional to its size, so the SUV of smaller metastatic lymph nodes is often low and more difficult to detect by PET/CT[15]. In other words, PET/CT has lower sensitivity and higher specificity for distant metastatic lymph nodes than contrast-enhanced CT.

Pseudomonas aeruginosa injection is performed using attenuated Pseudomonas aeruginosa. Previous studies have confirmed that injection of Pseudomonas aeruginosa has a significant effect on improving postoperative lymphatic leakage of...
Table 2 Information from this case report organized into a timeline

| Time lane                        | Events                                                                 |
|----------------------------------|------------------------------------------------------------------------|
| June 3, 2020                     | The male presented with a left cervical mass for one month             |
| June 9, 2020                     | Lymph node biopsy was performed and histopathological examination revealed that the metastatic adenocarcinoma was found in the tissue |
| June 18, 2020                    | The patient underwent gastroenteroscopy and the results revealed that one pedunculated polyp with mucosal erosion was observed in sigmoid colon, and histological examination revealed that adenocarcinoma was found in the intramucosal tissue |
| June 30, 2020 to September 30, 2020 | Undergoing 6 cycles of chemotherapy with FOLFOX + cetuximab regimen   |
| October 22, 2020                 | The resection of sigmoid carcinoma and mesenteric lymph node dissection were performed. Histological examination showed moderately differentiated adenocarcinoma localized in the mucosa, and one of five paracolic lymph nodes contained metastatic carcinoma (ypT1N1M1) |
| November 30, 2020 to January 30, 2021 | Undergoing 4 cycles of chemotherapy with FOLFOX + capecitabine regimen |
| February 24, 2021                | Virchow lymph node dissection was selected by mutual consultation between the patient and us |
| February 25, 2021 to March 5, 2021 | Postoperative lymphatic leakage                                       |
| March 24, 2021-So far            | The patient received chemotherapy with capecitabine and cetuximab. At nearly half of a year following the surgery, the patient was asymptomatic, and there were no signs of tumor recurrence or progression |

FOLFOX: Fluorouracil, leucovorin and oxaliplatin.

thyroid cancer[16]. The possible mechanism is as follows: Pseudomonas aeruginosa can penetrate into the subcutaneous space and produce aseptic inflammation, which promotes the closure of lymphatic vessels and reduces lymphatic leakage. In our case, the patient developed a lymphatic fistula after supraclavicular lymph node dissection. After the failure of a series of conservative treatments, we attempted to inject Pseudomonas aeruginosa from the left venous angle to reduce lymphatic leakage and achieved good results.

CONCLUSION

In summary, isolated Virchow’s lymph node metastasis is a potential metastatic route of CRC. In addition, when supraclavicular lymph node metastases are controlled by chemotherapeutic drugs, radical resection of both the primary site and the metastatic lesion is feasible. However, there is a need for further research to determine the optimum duration of preoperative chemotherapy and to further perfect surgical interventions.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

2. Byun JH, Ahn JB, Kim SY, Kang JH, Zang DY, Kang SY, Kang MJ, Shim BY, Baek SK, Kim BS, Lee KH, Lee SI, Cho SH, Sohn BS, Kim S, Hwang IG, Nam EM, Seo BG, Oh SC, Lee MA, Lee SC, Hong JH, Park YS. The impact of primary tumor location in patients with metastatic colorectal cancer: a Korean Cancer Study Group CO12-04 study. *Korean J Intern Med* 2019; 34: 165-177 [PMID: 29172407 DOI: 10.3904/kjim.2016.348]

3. Takahashi S, Iiia T, Shimada Y, Kobayashi Y, Sada K, Iwaya A, Maruyama S, Tani T, Hatakeyama K. [A long-term survival case of far-advanced colon cancer with Virchow’s lymph node and lung
metastasis that responded to multidisciplinary therapy]. Gan To Kagaku Ryoho 2009; 36: 127-129 [PMID: 19151578]

4 Hirose H, Ikeda M, Miyoshi N, Kim HM, Okano M, Uemura M, Yamashita S, Takemasa I, Mizushima T, Yamamoto H, Ishii H, Sekimoto M, Doki Y, Mori M. [A long-term survival case of rectal cancer with Virchow’s lymph node metastasis by multimodality therapy]. Gan To Kagaku Ryoho 2010; 37: 2545-2547 [PMID: 21224634]

5 Ando M, Fujiya K, Kamikozuru H, Ganno H, Amagase H, Takeuchi S, Kawai Y, Fukuda A, Nagahama T, Ami K, Aoki N, Arai K, Tei S, Okada Y, Miura K. [Long-term survival of a case with advanced sigmoid colon cancer and Virchow’s lymph node metastasis]. Gan To Kagaku Ryoho 2013; 40: 2083-2085 [PMID: 24394020]

6 Suliman MS, Singh M, Ajmeri AN, Stuart DL, Teka ST. Virchow’s node: a case report of an extremely rare presentation of metastasis of adenocarcinoma with mucinous features from the colon. Int J Gen Med 2019; 12: 137-140 [PMID: 31114290 DOI: 10.2147/IJGM.S201617]

7 Achmad H, Hanifa R. Supraclavicular Lymphnodes: Unusual Manifestation of Metastases Adenocarcinoma Colon. Acta Med Indones 2015; 47: 333-339 [PMID: 26932703]

8 Das S, Ladell DS, Podgrabiniska S, Ponomarev V, Nagi C, Fallon JT, Skobe M. Vascular endothelial growth factor-C induces lymphangitic carcinomatosis, an extremely aggressive form of lung metastases. Cancer Res 2010; 70: 1814-1824 [PMID: 20179201 DOI: 10.1158/0008-5472.CAN-09-3675]

9 Aghili M, Izadi S, Madani H, Mortazavi H. Clinical and pathological evaluation of patients with early and late recurrence of colorectal cancer. Asia Pac J Clin Oncol 2010; 6: 35-41 [PMID: 20398036 DOI: 10.1111/j.1743-7563.2010.01275.x]

10 Aghili M, Izadi S, Madani H, Mortazavi H. Clinical and pathological evaluation of patients with early and late recurrence of colorectal cancer. Asia Pac J Clin Oncol 2010; 6: 35-41 [PMID: 20398036 DOI: 10.1111/j.1743-7563.2010.01275.x]

11 Weitz J, Koch M, Debuts J, Höhler T, Galle PR, Bücheler MW. Colorectal cancer. Lancet 2005; 365: 153-165 [PMID: 15639209 DOI: 10.1016/S0140-6736(05)17706-X]

12 Siegel R, DeSantis C, Ward EM. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012; 62: 220-241 [PMID: 22700443 DOI: 10.3322/caac.21149]

13 Watanabe M, Ito K, Kozuki R, Toi T, Takahashi K, Okamura A, Imamura Y. Recent progress in multidisciplinary treatment for patients with esophageal cancer. Asia Pac J Clin Oncol 2010; 6: 35-41 [PMID: 20398036 DOI: 10.1111/j.1743-7563.2010.01275.x]

14 Blodgett TM, Meltzer CC, Townsend DW. PET/CT: form and function. Radiology 2007; 242: 360-385 [PMID: 17255408 DOI: 10.1148/radiol.242051113]

15 Kwak JY, Kim JS, Kim HJ, Ha HK, Yu CS, Kim JC. Diagnostic value of FDG-PET/CT for lymph node metastasis of colorectal cancer. World J Surg 2012; 36: 1898-1905 [PMID: 22526032 DOI: 10.1007/s00268-012-1575-3]

16 Chen Q, Chen Y, Sa A, Ma Y, Yu B, Zou X, Peng D, Zhu J. Ultrasound-guided percutaneous injection of Pseudomonas aeruginosa mannose sensitive hemagglutinin for treatment of chyle fistula following neck dissection: Two case reports. Medicine (Baltimore) 2020; 99: e18816 [PMID: 32003385 DOI: 10.1097/MD.0000000000018816]
