Clinical Case Report

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Successful chemotherapeutic treatment for metastatic littoral cell angioma

A case report

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Abstract

Rationale: Metastatic littoral cell angioma (LCA) is extremely rare. No standard therapeutic strategy has been established, and the impact of chemotherapy has not yet been evaluated.

Patient concerns: A 61-year-old woman was admitted because of bicytopenia. She had a splenectomy for LCA of the spleen 10 years earlier. Bone marrow aspiration was normal, and a computed tomography (CT) scan showed hepatomegaly with multiple liver tumors.

Diagnoses: Liver biopsy samples showed macrophage-like cell infiltration in the hepatic sinusoids. Metastatic LCA was diagnosed based on immunohistochemistry, imaging tests, and the clinical course.

Interventions: Immunosuppressive agents, such as prednisolone and cyclosporine, were ineffective. Next, cytotoxic agents, such as etoposide, paclitaxel, and vincristine, were administered.

Outcomes: Cytotoxic agents showed a prominent effect against LCA. CT showed improvement of the hepatomegaly, and fluoro-deoxyglucose (FDG) uptake decreased markedly at a follow-up FDG- positron emission tomography (PET) scan.

Lessons: Chemotherapeutic treatment based on hemophagocytic syndrome or angiosarcoma might have anti-tumor activity against metastatic LCA. Analysis of the molecular characteristics of this tumor is needed to develop better treatment options.

Abbreviations: CT = computed tomography, CTCAE = common terminology criteria of adverse events, FDG = fluoro-deoxyglucose, LCA = littoral cell angioma, PET = positron emission tomography, RBC = red blood cell, sIL-2R = soluble IL-2 receptor, VEGFR = vascular endothelial growth factor receptor.

Keywords: etoposide, fluoro-deoxyglucose-positron emission tomography, hemophagocytic syndrome, littoral cell angioma, paclitaxel

1. Introduction

Littoral cell angioma (LCA) is a rare benign vascular tumor that originates from splenic sinus lining cells. In 1991, Falk et al[1] first reported 17 cases of LCA. In 2016, Peckova et al[2] analyzed 25 cases of LCA and reported that LCA shows neither a sex nor an age predilection and is associated with visceral malignancies (60%), such as colorectal cancer and renal cell carcinoma. This tumor grows slowly and is diagnosed incidentally in most cases. The characteristic finding of LCA is that the tumor cells have both endothelial and histiocytic phenotypes, and typically these cells are positive for cluster of differentiation 31 (CD31), factor VIII, Ets-related gene (ERG), cluster of differentiation 68 (CD68), and cluster of differentiation 163 (CD163), and negative for CD34 and Wilms tumor-1.[3] Since the tumor cells have a histiocytic phenotype, this tumor is occasionally associated with hemophagocytosis, and anemia or thrombocytopenia might become a clue to the diagnosis of this disease.[4–6]

LCA is essentially a benign tumor and seldom metastasizes to other organs, and there are very few case reports of metastatic LCA. Surgical resection is the only therapeutic option for this disease, and there is no effective chemotherapy for metastatic LCA.

This is the first report of chemotherapeutic agents that were effective against metastatic LCA in past 20 years.

2. Case presentation

A 61-year-old woman was admitted to our hospital because of bilateral lower extremity edema, fatigue, anemia, and thrombocytopenia. She had been admitted to another hospital because of

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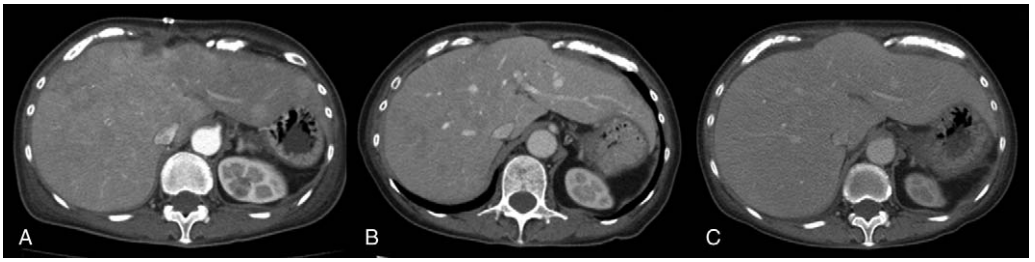

Figure 1. A, Computed tomography shows hepatomegaly and multiple liver tumors. B, Tumor shrinkage and the improvement of hepatomegaly are seen after treatment with etoposide. C, Hepatomegaly is again observed after failure of paclitaxel chemotherapy.

thrombocytopenia, and a splenic tumor was resected 10 years earlier; the diagnosis was LCA of the spleen. Complete blood count values showed anemia (hemoglobin 10.4 g/dL) and severe thrombocytopenia (platelets $3.4 \times 10^4/\mu L$). Neither petechiae nor purpura was detected on her skin. Coagulation tests were within normal limits. Soluble IL-2 receptor (sIL-2R) (19534.0 U/mL) and ferritin (5611.6 ng/mL) were extremely high, and other tumor markers (CEA, CA19–9, AFP) were within normal limits. Bone marrow aspiration showed normo-hypocellular bone marrow with no atypical cell aggregates. Computed tomography (CT) showed hepatomegaly with multiple liver tumors (Fig. 1A) and periportal lymphadenopathy. The density of these tumors was high in the early phase and low in the late phase of contrast-enhanced CT. FDG-PET showed abnormal FDG uptake in the liver tumors and in the periportal lymph nodes (Fig. 2A). An upper gastrointestinal series showed no significant lesions. To confirm the diagnosis, 2 liver tissue samples were obtained by open surgery. Hematoxylin and eosin staining showed oval cells with oval nuclei and multivacuolated cytoplasm proliferating within the sinusoid (Fig. 3A and B). Immunohistochemically, these cells were positive for CD31, CD68, and CD163, but negative for CD34, factor VIII, ERG, hepatocyte, AE1/AE3, alpha-SMA, desmin, and S-100 protein (Fig. 3C and D). Hemophagocytosis by these atypical cells was suggested. Although mitotic figures were not evident, and endothelial markers such as factor VIII and ERG were negative, the diagnosis of metastatic LCA recurrence was made based on the clinical course and imaging findings.

First, paclitaxel (80 mg/m^2, days 1, 8, 15, q4w) was given based on the treatment of angiosarcoma. After administration of paclitaxel on day 1 and day 8, platelet counts increased, but red blood cell (RBC) counts were not increased. Therefore, cyclosporine and prednisolone (1 mg/kg) were administered based on hemophagocytic syndrome, but these agents showed no effect. Then, etoposide (VP-16 150 mg/m^2, days 1, 3, 8, 10, 15 followed by weekly) was added. However, she developed prolonged leukopenia of common terminology criteria of adverse events (CTCAE) grade 4, and the schedule was changed to biweekly administration at a dose of 120 mg/m^2. After adding etoposide, RBC and platelet counts increased, and sIL-2R was decreased.

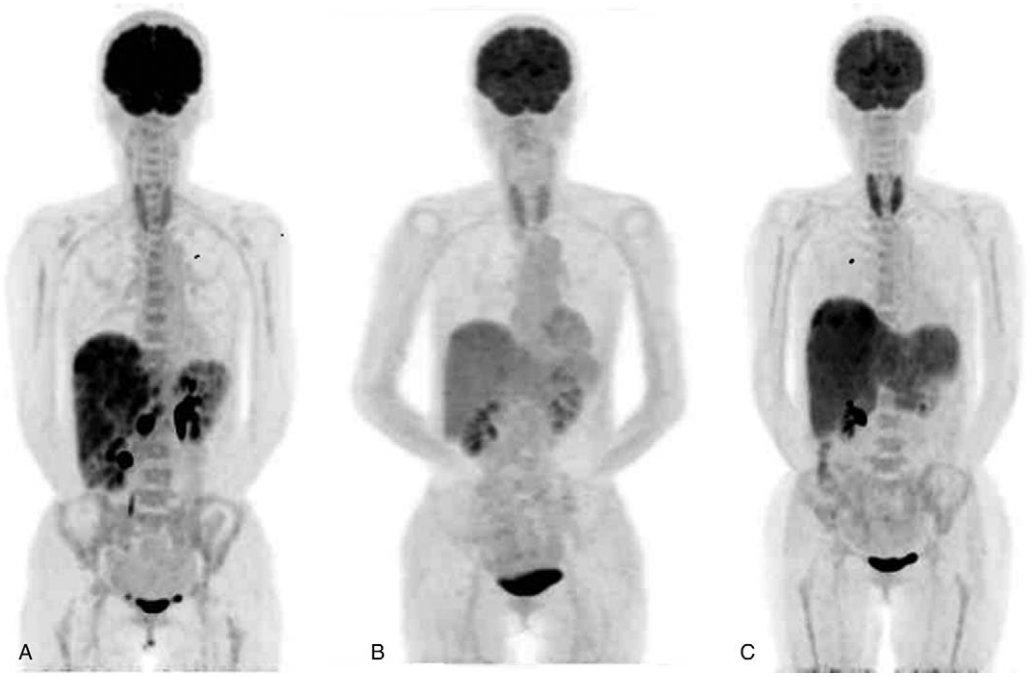

Figure 2. A, FDG-PET examination shows increased FDG uptake in the liver tumors and in the periportal lymph nodes. B, FDG uptake is markedly decreased after treatment with etoposide. C, Abnormal FDG uptake is observed after failure of paclitaxel chemotherapy. FDG = fluoro-deoxyglucose, PET = positron emission tomography.

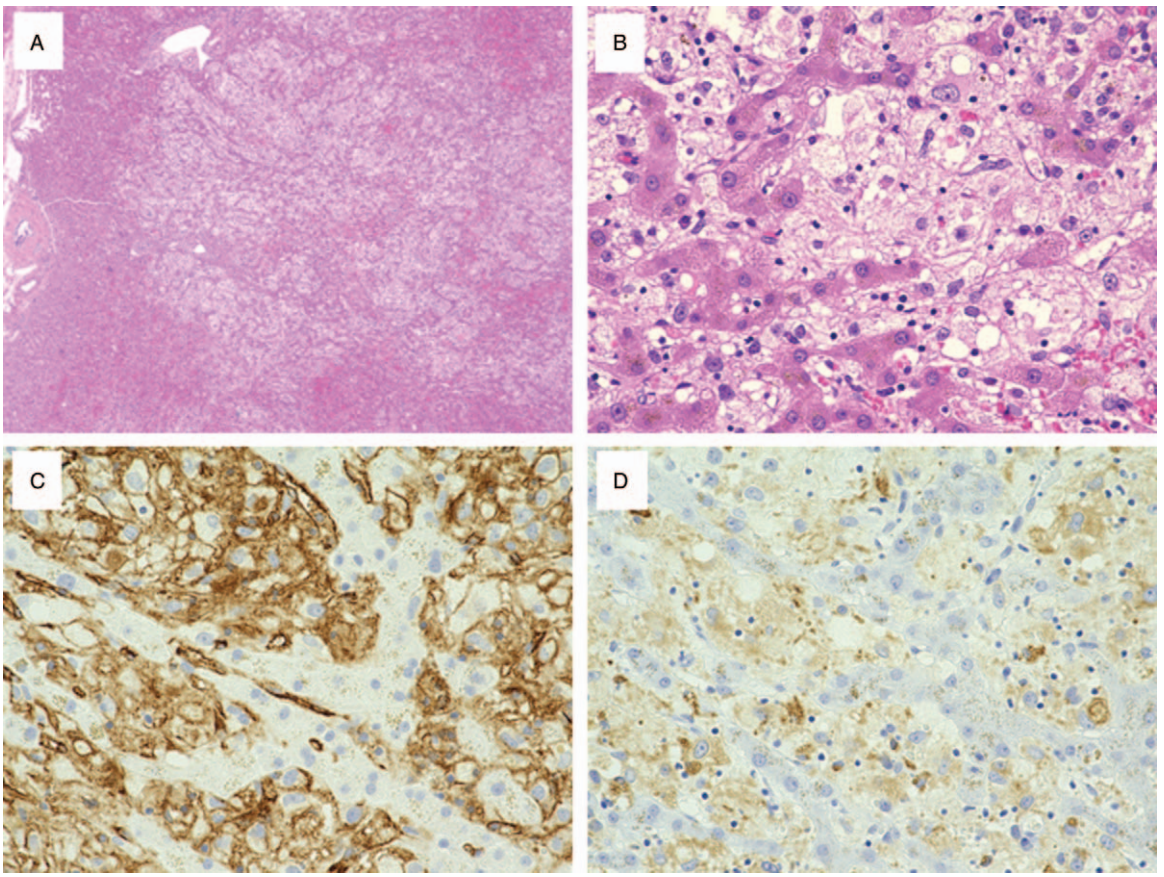

Figure 3. Hematoxylin and eosin staining shows macrophage-like cell infiltration in the hepatic sinusoids. (A: ×40, B: ×400). The macrophage-like cells are positive for CD31 (C) and CD68 (D).

CT showed improvement of the hepatomegaly, and FDG uptake decreased significantly in the liver and lymph nodes on a follow-up FDG-PET scan (Figs. 1B and 2B). Five months later, the platelet count was again decreased, and she was switched to paclitaxel (80 mg/m^2, days 1, 8, 15, q4w). Because of prolonged neutropenia of CTCAE grade 4, the schedule was changed to biweekly administration at a dose of 80 mg/m^2. After one cycle of chemotherapy, the platelet count was increased to $5 \times 10^4/\mu L$.

Four months later, she complained of fatigue, and complete blood count values showed anemia (5.2 g/dL) and thrombocytopenia ($3.1 \times 10^4/\mu L$). CT showed hepatomegaly, and FDG-PET again showed high FDG uptake in the liver (Figs. 1C and 2C). Vincristine (1 mg, biweekly) was then given as the third-line chemotherapy, and her fatigue soon improved. She did not need transfusion, and CT showed improvement of the hepatomegaly. However, after 6 doses of vincristine, she could not continue the therapy because of peripheral neuropathy.

Doxorubicin was then administered, but she refused to continue the therapy because of adverse events such as nausea and fatigue, and she died of hemorrhagic cerebral infarction 21 months after the diagnosis of metastatic LCA (Fig. 4).

Written, informed consent was obtained from the patient for the publication of the case details.

3. Discussion

Since this patient showed marked bicytopenia, hematological malignancies were first suspected, but no hematological abnormalities were detected on bone marrow aspiration. Liver biopsy samples showed macrophage-like cell infiltration in the hepatic sinusoids. Hemophagocytosis by these atypical cells was detected, and thus secondary hemophagocytic syndrome also had to be ruled out. Secondary hemophagocytic syndrome is associated with infectious diseases, autoimmune diseases, and malignancies, such as malignant lymphoma, prostate cancer, and lung cancer. Hemophagocytic syndrome typically presents with systemic inflammation, but the present patient had no fever, and C-reactive protein was not significantly elevated. In addition, macrophage-like cells were present only in the liver, not in other organs including the bone marrow. Epstein-Barr virus and cytomegalovirus are the most common causes of virus-associated hemophagocytic syndrome, but active infection with these viruses was not evident immunologically. No other malignancies were detected by imaging and pathological examinations. This patient had no symptoms suggestive of autoimmune diseases, and autoantibodies were not detected. Therefore, secondary hemophagocytic syndrome was unlikely.

Because mitotic figures and multi-nucleated giant cells were not seen in liver specimens, a malignant tumor could not be diagnosed pathologically. However, FDG-PET showed marked FDG uptake in liver tumors, suggesting the malignant potential of these tumors. Because LCA is essentially a benign tumor, these macrophage-like cells might not show a strong malignant phenotype pathologically. With these, the diagnosis of metastatic LCA was made clinically. Typical LCA expresses both endothelial markers (CD31, factor VIII) and histiocytic markers (CD68). CD21 is also expressed in LCA, and this distinguishes LCA from other vascular tumors, such as splenic hemangioma

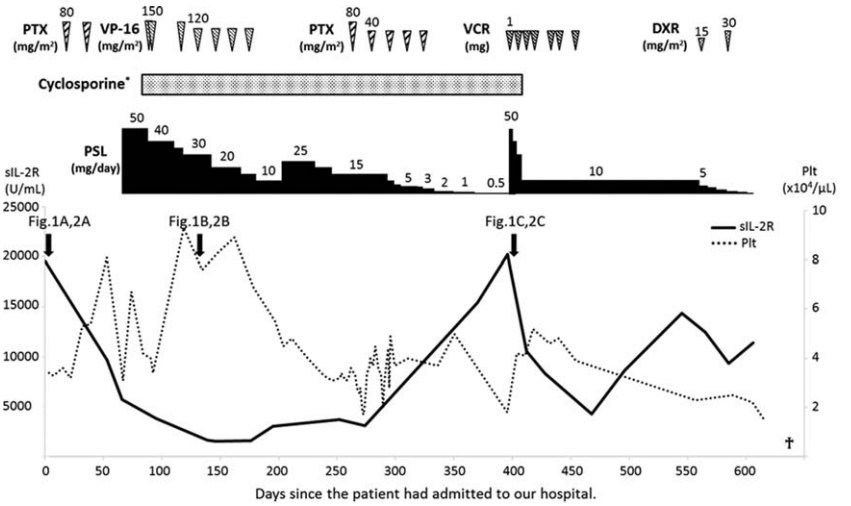

Figure 4. Clinical course and variations in serum soluble IL-2 receptor (sIL-2R) and platelet counts (Plt). *The start dose of cyclosporine was 100 mg/d, and then the dose of cyclosporine was adjusted so that the trough level was 150 to 200 ng/mL. DXR = doxorubicin, PSL = prednisolone, PTX = paclitaxel, VCR = vincristine, VP-16 = etoposide.

and angiosarcoma.[7] The macrophage-like cells in the liver were positive for CD31, CD68, and CD163, but negative for factor VIII and ERG. These tumor cells might lose their endothelial phenotype through the process of acquiring metastatic potential.

An FDG-PET scan is a useful imaging test to evaluate cancer progression and the effect of chemotherapy. In this case, an FDG-PET scan showed high FDG-uptake in the liver tumors at diagnosis, and FDG uptake decreased significantly after the treatment with chemotherapeutic agents. The utility of an FDG-PET scan at diagnosis of LCA has not been studied, but the present case suggested its utility for diagnosis and for evaluation of the treatment effect.

LCA seldom metastasizes to other organs, and surgical resection is the only therapeutic approach. There have been some case reports of metastatic LCA,[7–9] but there is no case report concerning the impact of chemotherapy on metastatic LCA to the best of our knowledge. Because this case showed a prominent histiocytic phenotype leading to hemophagocytosis, the patient was first treated with prednisolone and cyclosporine. However, these immunosuppressive agents showed minimal effect against LCA. This is because hemophagocytosis was not induced by hypercytokinemia due to other malignancies, viral infection, or autoimmune diseases. On the other hand, chemotherapeutic agents, such as etoposide, paclitaxel, and vincristine showed a prominent anti-tumor effect. This also supports the neoplastic proliferation of these macrophage-like cells. Because etoposide is often used for both hemophagocytic syndrome and histiocytic malignancies, and paclitaxel is the standard chemotherapeutic agent for angiosarcoma, the treatment strategy for histiocytic sarcoma or angiosarcoma may be recommended in LCA. However, doxorubicin, which is the standard chemotherapeutic agent for sarcoma including histiocytic sarcoma, showed no effect in this case.

Though the chemotherapeutic agents were effective, it was difficult to continue cytotoxic chemotherapy because of adverse events, especially cumulative adverse events such as neuropathy. We need to develop new treatment strategies. Recently, Peckova et al[2] reported that LCA expresses vascular endothelial growth factor receptor (VEGFR) -2 and -3. Considering the endothelial phenotypic characteristics of LCA, VEGFR might have an important role in LCA cell survival, and multi-kinase inhibitors, such as pazopanib, sunitinib, and sorafenib, might have an anti-tumor effect in metastatic LCA. Moreover, this case showed multiple liver metastases, but no metastatic lesions were detected in other organs, including lung and bone marrow, and liver transplantation was considered. This might be due to the cell attachment between metastatic LCA cells and sinusoid endothelial cells. Understanding the expression of cell adhesion molecules might help identify the treatment target of this rare disease.

Author contributions

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