Mast Cell Sarcoma of the Retroperitoneum With Concurrent Systemic Mastocytosis and an Undisclosed Associated Hematologic Neoplasm: A Case Report

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ABSTRACT: Mastocytosis is a rare disorder affecting both children and adults by gathering of functionally defective mast cells in the body's tissues. The World Health Organization (WHO) classified mastocytosis into cutaneous mastocytosis, systemic mastocytosis (SM), and mast cell sarcoma (MCS). We hereby present a case of retroperitoneal MCS with concurrent systemic mastocytosis and an undisclosed associated hematological neoplasm (SM-undisclosed AHN). The diagnosis of MCS and SM was made after the second biopsy over retroperitoneal mass, lymph node, and ovary for rapidly progressive disease with the presentation of unexplained recurrent flushing, palpitation, and shock, in addition to abdominal pain. A clonal myeloid neoplasm was also suspected by the karyotype and hemogram data. Unfortunately, the patient succumbed to the disease quickly. Apart from this unique case, the previously reported cases of SM with MCS in the literature were also reviewed.

KEYWORDS: Systemic mastocytosis, mast cell sarcoma, retroperitoneum, associated hematological neoplasm

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Introduction

Mastocytosis arises from a clonal, neoplastic proliferation of mast cells that accumulate in one or more organ systems.[1] Mast cell sarcoma (MCS) is an exceedingly rare variant of mastocytosis identified by morphologically atypical mast cells that are locally destructive and highly aggressive.[2] We hereby present a unique case of retroperitoneal MCS with concurrent systemic mastocytosis. An associated hematological neoplasm, suspected to be a clonal myeloid disorder, is also noted.

Case Presentation

A 23-year-old adult was a case of 46, XY disorder of sex development (46 XY DSD) (so-called male pseudohermaphrodite). Before DSD was diagnosed by karyotype analysis in May 2020, she had suffered from intermittent facial flushing and palpitation associated with tachypnea and near syncope for 2 months. Hormone replacement therapy was tried but without improvement.

Four months later, abdominal magnetic resonance imaging (MRI) revealed bulky retroperitoneal and retrocrural lymphadenopathies when she had intermittent abdominal pain and body weight loss of 5 kg for 2 weeks, in addition to persistent intermittent flushing and palpitation. Subsequent pathology interpretation of computed tomography (CT)-guided biopsy of retroperitoneum mass was spermatocytic seminoma according to morphologic pictures (Figure 1) and the expression of CD30 and CD117 immunohistochemically. The *SRY* mutation (c.60delT), responsible for DSD, was confirmed soon thereafter.

For the treatment of spermatocytic seminoma, the patient underwent one course of chemotherapy with bleomycin, etoposide, and cisplatin. After chemotherapy, the patient had temporary relief of abdominal pain, but symptoms recurred soon after. One episode of flushing and palpitation, followed by shock with conscious change and seizure, occurred during hospitalization. The patient recovered quickly and no specific etiology could be identified. At the same time, we noticed that regular antihistamines and antipyretics as needed could relieve her palpitation and flushing. Considering all these atypical presentations, open biopsy was suggested.

A few days later, oliguria was noted, along with elevated creatinine (2.42 mg/dL), uric acid (11.2 mg/dL), and LDH (1383 U/L). Incisional biopsy over the right pelvic lymph node (LN), right ovary, and retroperitoneal tumor and bilateral double-J catheter placement for obstructive nephropathy caused by tumor compression was performed. Her renal function improved temporarily after the surgery; however, only days after the operation, oliguria, dyspnea, pulmonary edema, and pleural effusion were found. An abdominal CT scan found multiple new liver metastases, and progressive retroperitoneal tumors with necrosis. Shock and consciousness change developed suddenly 2 days later. No evidence of brain metastases but a 2.6 × 0.5 cm lesion over the left occipital scalp with bony erosion was revealed on brain CT scan.

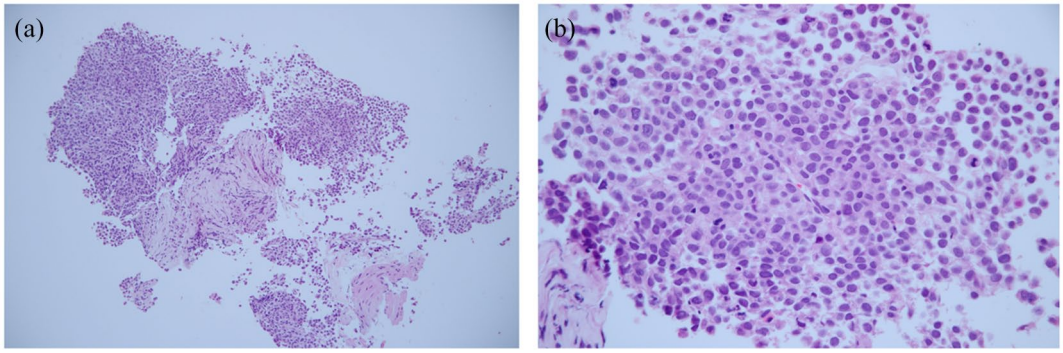

Figure 1. The morphology of the specimen from biopsy of retroperineum mass shows a picture of proliferation of neoplastic cells in sheet pattern with adjacent loose stromal tissue having inflammatory cells infiltration, including lymphocytes and eosinophils (a and b).

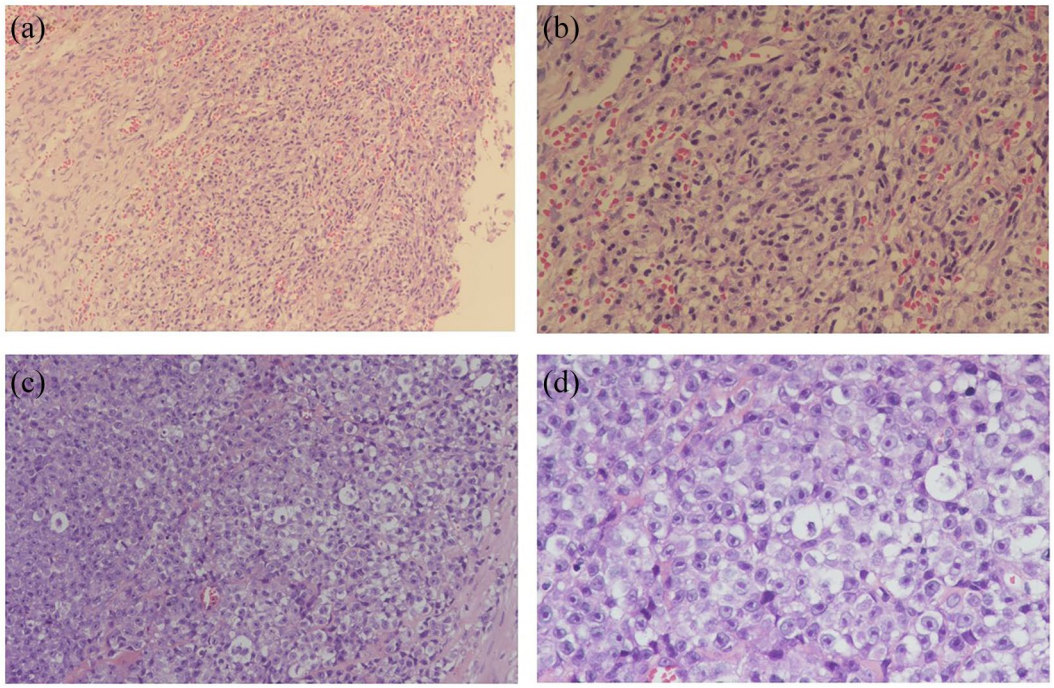

Figure 2. Morphologically, the tumor cells of ovary show diffuse infiltration of mast cells with spindle shapes (a and b). The tumor cells of retroperitoneum show diffuse infiltration of atypical round-shaped epithelioid tumor cells, with the majority showing prominent nucleoli and eosinophilic to amphophilic cytoplasm, while scattered cells have hyperchromatic nuclei without nucleoli located peripherally resembling mast cells (c and d).

Mastocytosis in ovarian tissue was reported first (Figure 2a and b). Meanwhile, bone marrow aspiration was suggested for progressive unexplainable leukocytosis during this month (white cell count 34 700/μL with neutrophils 84.8%, lymphocytes 5.6%, monocytes 1.5%, eosinophils 2%, and metamyelocytes 3%, hemoglobin 8.9 g/dL and platelets 169 000/μL on the day of conscious change). However, her family refused. Her condition went downhill rapidly, and the distributive shock became refractory 2 days after conscious change (1 week after biopsy). The patient expired on the following day.

The final pathological reports of the retroperitoneal tumor and LN were confirmed shortly after the patient's death. Morphologically, there were diffuse infiltrations of atypical round-shaped epithelioid tumor cells, with the majority showing prominent nucleoli and eosinophilic to amphophilic cytoplasm, while scattered cells had hyperchromatic nuclei without nucleoli located peripherally resembling mast cells (Figure 2c and d). Conspicuous tumor necrosis s also noted in the retroperitoneal specimen. Immunohistochemistry staining (IHC) showed diffuse positivity for CD117, CD30, CD33, CD43, tryptase and focal positive for CD25, CD68 and negative for CD2, myeloperoxidase and lysozyme (Figure 3). The neoplastic cells in LN were also diffusely positive for CD117 and tryptase immunostaining. Therefore, the diagnosis of SM with retroperitoneal MCS was impressed. In addition, the C-kit mutation D816V was demonstrated in retroperitoneal tumor, pelvic LN, and ovary. The serum tryptase level before death was >200 μg/lL. Karyotype of peripheral blood checked on her final day revealed 46 to 54, XY, -1, +2, +rea(4q), +5, +6, rea(12q), rea(13p), -14, add(14)(p10), add(15)(p10), i(17)

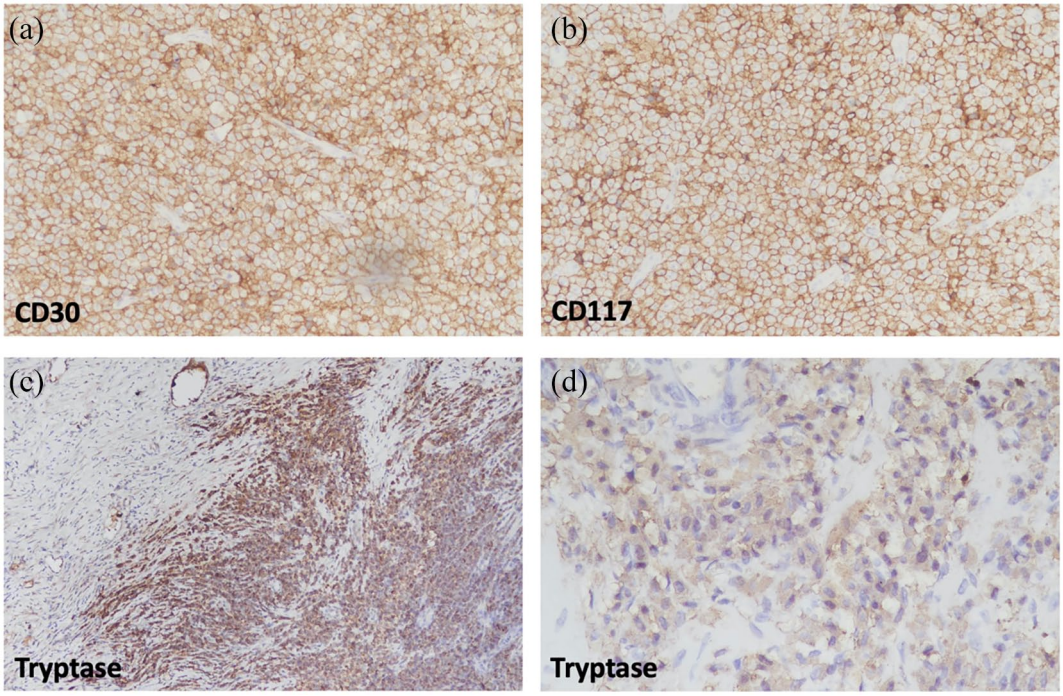

Figure 3. Immunohistochemically, the tumor cells of retroperitoneal specimens show strong positivity for CD30 (a), CD117 (b), and strong and diffuse positivity for mast cell tryptase (c). The tumor cells of ovarian specimens show diffuse expression of mast cell tryptase (d).

(q10), +19, +del(20)(q13.1), –21, –22, +2~6 marker chromosome among 6 of 20 cells, indicative the possibility of a clonal myeloid neoplasm.

Discussion

Although MCS was described as early as 1986 by Horny et al,[3] the diagnosis of MCS remains challenging. The morphology of MCS is highly heterogeneous and may differ from site to site within the same patient.[2] Likewise, IHC in MCS is complicated. In MCS, highly atypical mast cells usually express tryptase, CD117, and CD68 and are negative for CD25 in 25% of the cases and negative for CD2 in 48% of the cases.[2] CD30, which has been suggested as a marker for SM aggressiveness, is expressed in 42% of tested MCS samples.[2] In our case, the initial pathological diagnosis of a retroperitoneal mass was misled as spermatocytic seminoma because of the history of DSD, location of the lesion and indistinctive morphological and IHC features. The clue leading us to the suspicion of MCS for retroperitoneal mass was diffuse mast cell infiltration in the ovary sample. Notably, despite the high sensitivity and specificity of tryptase in MCS, it is possibly only stained under a special stain protocol.[4] Similarly, tryptase staining in our case was much stronger after recombining the reagents. Therefore, the presence of atypical cells positive for CD117 and/or tryptase could lead to the proper suspicion of MCS, which is the major step of correct diagnosis.[2]

The diffused infiltration of spindle-shaped mast cells in ovary not only guided us to the diagnosis of MCS, but also fulfilled 1 major and 1 minor criterion of SM. The spectrum of systemic mastocytosis was broad. According to the WHO diagnostic criteria for SM, our case fulfilled 1 major SM criterion and 3 minor criteria, including spindle-shaped mast cells in extracutaneous tissues, mutational analysis of KIT showing codon 816 mutation, and extracutaneous mast cells expressing CD25. Thus, the diagnosis of SM was confirmed, but could not be classified as aggressive SM because concurrent MCS masked the possible presentation of aggressive SM. In addition, the progressive and unreasonable leukocytosis (neutrophilia 29 426/μL but not mast cells in peripheral blood) represents the existence of bone marrow disorder per se. Due to the patient's refusal of bone marrow examination, the exact diagnosis of bone marrow disorder could not be obtained, nor could aleukemic mast cell leukemia or bone marrow involvement of MCS or SM be excluded.[5] Nevertheless, much evidence can be drawn from the karyotype of peripheral leukocyte, which is indicative of chronic myeloid leukemia (the presence of i(17)), myeloproliferative disorder (the presence of i(17) and del(20)), myelodysplastic syndrome (the presence of i(17), del(20) and +19), or even acute myeloid leukemia (the presence of i(17), del(20) and +19).[6] Taken together with extreme neutrophilia, a clonal myeloid neoplasm is postulated. Taking into account of the concurrent diagnosis of SM and suspected clonal myeloid neoplasm, the final diagnosis of SM-AHN was made.

This case demonstrates the features of both SM and MCS. Of the 26 cases of MCS published in the literature, only 4 had a history of associated SM.[4,7-9] The first was a case of aggressive SM with sarcoma-like growth of mast cells in the skeleton, and progression to mast cell leukemia.[4] The second was a case of MCS of the scalp, which appeared to be the first

manifestation of underlying SM.[7] The third was a case of aggressive SM associated with chronic eosinophilic leukemia with transformation into a "secondary" bifocal MCS over the colon and liver.[8] Last, there was a case of bone marrow mastocytosis with an associated secondary extramedullary MCS over the retroperitoneum, testis, and heart, proven by autopsy.[9] Therefore, just as how MCS could lead a progressive course to transform into an aggressive generalized disease; it could also be an initial presentation of a systemic disease. In addition, while somatic *KIT* mutations are detected in 90% of SM,[10] 50% of cases of MCS have wild-type *KIT*.[2] The most common *KIT* mutation is D816V, which was also detected in neoplastic mast cells from the ovary, pelvic LN, and retroperitoneal mass in our patient.

Taken together, it is proposed that our patient had SM with secondary MCS. A subcategory of secondary MCS is not included in the WHO classification,[1] but the term "secondary" MCS has been used to describe the case of SM with transformation to MCS.[4,9] Our case developed a clonal myeloid neoplasm in a short time after the clinical onset of MCS. Although the *KIT* D816V mutation could be detected in clonal hematological non-mast cells in SM-AHN (30% and 20% cases of SM-acute myeloid leukemia (SM-AML) and SM-MPN respectively),[10] the *KIT* status of blood cells in our case was not checked. An abnormal karyotype, found in 26% of cases with SM-AHN but uncommon in SM,[11] corresponds to our situation. Therefore, the mechanism of SM, MCS and a non-MC hematological neoplasm transformation is unclear, but studies support a multi-hit theory in developing SM-AHN, and *KIT* mutation might occur before, or more often, after the non-*KIT* mutation.[12] Due to the complexity of the mechanism, multiple organ involvement, and convoluting clinical course of mast cell disorders, collaborative multidisciplinary patient care and pooling of experience and knowledge from different specialty is crucial for making the correct diagnosis and arranging optimal and timely treatment.[13]

In summary, we present a unique case of MCS with concurrent systemic mastocytosis and an undisclosed associated hematological neoplasm (SM-undisclosed AHN), with a rapidly progressing disease burden eventually leading to mortality. Despite unknown bone marrow status at disease burden, it is worth noting that our case draws attention to a subvariety of SMs that may progress to MCS, rapidly accompanied by the existence of an associate hematological neoplasm.

Author Contributions

Ing Chen and Ming-Yun Hsieh wrote the manuscript and performed the literature review. Jung-Chia Lin provided the figures with interpretation. Jia-Bin Liao and Pin-Pen Hsieh were responsible for the pathological diagnoses. Jia-Bin Liao, Pin-Pen Hsieh, and Ming-Yun Hsieh reviewed and revised the manuscript. All authors read and approved the final manuscript.

Ethics Statement

The report received ethical approval from the institutional review board (IRB) of Veterans General Hospital of Kaohsiung. IRB No.: KSVGH21-CT6-11.

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