Aggressive systemic mastocytosis mimicking lymphoma: a case report

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Case Report

Keywords: Aggressive systemic mastocytosis, Mast cell, CD25, KIT

Posted Date: December 30th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-135231/v1>

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Abstract

Background

Aggressive systemic mastocytosis (ASM) is a very rare form of systemic mastocytosis (SM). The diagnosis of ASM requires the presence of SM criteria with C finding and does not meet the criteria for mast cell leukaemia. Herein, we report an ASM case that initially mimicked lymphoma based on clinical and radiographic analyses.

Case presentation:

A 87-year-old woman was admitted to our hospital due to the enlargement of cervical lymph nodes and weight loss. The lymph node biopsy is infiltrated by neoplastic mast cells with pale, faintly granular cytoplasm, and with reactive eosinophils in the lesions. The infiltrate is often para-follicular in distribution and the remnant of normal follicles can be seen. The neoplastic cell population was subsequently revealed to exhibit differentiation towards the mast cell lineage by expressing CD117 and CD25. Mutation analysis of c-KIT identified D816V mutation in exon 17.

Conclusion

ASM diagnosis can be challenging due to its rarity. This diagnosis can be confirmed or disregarded using immunohistochemical markers, such as CD117, CD2 and CD25, in combination with molecular analysis (KITD816V).

Background

Systemic mastocytosis (SM) is a heterogeneous disease characterized by the accumulation of neoplastic mast cells in one or more organ systems. In the revised 2016 WHO classification, mastocytosis was classified into cutaneous mastocytosis, SM and mast cell sarcoma, which was defined as a separate disease category [1]. Aggressive Systemic Mastocytosis (ASM), a rare subtype of SM, results from clonal proliferation and invasion of multiple organs by neoplastic mast cells. The clinical presentation varies, dependent on which organ systems are involved, and may take an indolent or rapidly fatal course. Here, we report a case of ASM with lymph nodes involvement as the first manifestation which mimicking lymphoma.

Case Presentation

An 87-year-old female presented to our hospital in January 2020 because of the enlargement of cervical lymph nodes, and weight loss of 10 kg over the previous 6 months. Physical examination showed the bilateral neck was obviously enlarged with a multinodular appearance, mild splenomegaly and ascites. There were no skin lesions or signs of chronic liver disease. Laboratory studies revealed white blood cell count of $4.5 \times 10^9/L$ with 40.5% eosinophils (with a normal differential count), red blood cell count of $3.25 \times 10^{12}/L$, a hemoglobin concentration of 97 g/L, and a platelet count of $48 \times 10^9/L$ (normal range, $100-300 \times 10^9/L$). The serum concentration of C-reactive protein was 12.52 mg/L (normally below 5 mg/L), and the serum tryptase level could not be assessed due to technical limitations. The tumor marker CA125 was present at a level of 54.4 U/mL (normal: <35 U/mL). Fluorine-18 fluorodeoxyglucose-enhanced positron emission tomography (FDG-PET) combined with Computed tomography (CT) scanning demonstrated abnormal accumulation of FDG with diffuse lymphadenopathy in the deep cervical space, posterior cervical triangle, bilateral supraclavicular fossa, mediastinum, bilateral axilla, porta hepatis, retroperitoneal and bilateral inguinal lymph nodes, splenomegaly with FDG metabolism, which considered as lymphoma. Increased metabolism of FDG in the fundus and body of stomach. Systemic osteoporosis, increased FDG metabolism in the bone marrow cavity and spinal degeneration.

A core biopsy on the left cervical lymph node was nondiagnostic and complete lymphadenectomy revealed the lymph node was diffusely infiltrated by neoplastic mast cells with abundant, lightly staining cytoplasm, and with reactive eosinophils in the lesions (Fig. 1a-1c). The infiltrate was often para-follicular in distribution and the remnant of normal follicles could be seen. A Giemsa stain revealed presence of increased mast cells in the received tissue. On immunohistochemistry, these neoplastic cells were positive for CD117 (Fig. 1d) and CD25 (Fig. 1e), and negative for CD2 (Fig. 1f), CD34, CD4, CD20, CD3, PAX5, CD68 (KP1 and PG-M1), MPO, CD35, CD21, CD23, CD163 and S-100. Gastrointestinal (GI) endoscopic biopsy showed mild chronic gastritis and the gastric biopsies were retrospectively stained for c-kit (Fig. 1g) and CD25 (Fig. 1h), revealing only a few scattered mast cells in the superficial lamina propria, confirming SM in the stomach. In situ hybridization for Epstein-Barr virus (EBV) encoding RNA (EBER) was negative. Polymerase chain reaction (PCR) plus sanger sequencing on lymph node tissue was positive for the KIT D816V mutation (Fig. 1i) and negative for PDGFRA mutation. Thus, our patient met the major criteria and three minor criteria. Based on the clinical, histologic, immunohistochemistry, laboratory findings and molecular features, a diagnosis of ASM was established. Using a next-generation sequencing (NGS) assay, we documented genomic alterations in KIT, and additional genetic abnormalities were ARID1A, BARD1, MYD88, TET2, KMT2C, POLE and RNF43 mutations, microsatellite instability high (MSI-H) and low tumor mutation burden. The details of genetic mutations in Table 1.

Table 1
Details of genetic mutations with aggressive systemic mastocytosis.

Gene	Amino Acid Change	Encoding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ARID1A	p.(Q1334del)	c.3999_4001delGCA	COSM298325	chr1:27100181	3.30%	NM_006015.5	nonframeshift Deletion
BARD1	p.(R378S)	c.1134G > C	rs2229571	chr2:215645464	48.25%	NM_000465.3	missense
MYD88	p.(L273P)	c.818T > C	COSM85940	chr3:38182641	2.55%	NM_001172567.1	missense
TET2	p.(K1468*)	c.4402A > T		chr4:106193940	24.89%	NM_001127208.2	nonsense
MAP3K4	p.(R157Hfs*29)	c.470_473delGTAAins AT		chr6:161469774	1.20%	NM_005922.3	frameshift Block Substitution
KMT2C	p.(Y816*)	c.2447_2448insA		chr7:151945071	28.70%	NM_170606.2	nonsense
KIT	p.(D816V)	c.2447A > T	COSM1314	chr4:55599321	18.35%	NM_000222.2	missense
POLE	p.(V1446Gfs*3)	c.2296 + 1delC	COSM85940	chr12:133220098	2.59%	NM_006231.3	frameshift Deletion
RNF43	p.(G659Vfs*41)	c.4337_4338delTG	COSM85940	chr17:56435160	1.92%	NM_017763.5	frameshift Deletion
AURKA	p.(I57V)	c.1976delG	rs1047972	chr20:54961463	99.70%	NM_003600.3	missense
AURKA	p.(F31I)	c.169A > G c.91T > A	rs2273535	chr20:54961541	48.20%	NM_003600.3	missense

Discussion

According to the most recent revised 2016 WHO classification[1], a diagnosis of SM could be made when the major criterion (≥ 15 MC in clusters) and / or 3 minor criteria (other extracutaneous organs > 25% of the mast cells infiltration, KIT mutation, CD25/CD2 co-expression,) are present. Due to the presence of C-findings (hypohemoglobinemia, thrombocytopenia, splenomegaly, and gastrointestinal dysfunction), a diagnosis of ASM was made. ASM is a hematopoietic neoplasm characterized by infiltration of visceral organs by neoplastic mast cells with consecutive organopathy and respective clinical and laboratory findings (so called C-Findings). In ASM the infiltration of mast cells causes impairment function of involved organs and the clinical picture is characterized by loss of function of involved organs. In our case, the patient has mild ascites, malabsorption, osteolysis and two cytopenia. The patient also presented with constitutional symptoms (weight loss), extensive lymphadenopathy, eosinophilia and splenomegaly, which mimicking a lymphoma. Lymph nodes involvement in ASM is common. Evidence of lymph nodes involvement includes lymphadenopathy. The main sign of lymph nodes involvement in ASM is the pathological accumulation of mast cells in the lymph nodes.

The histological pattern of the mast cell infiltrate can vary depending on the tissue sampled. On lymph node sample, mast cells aggregate predominantly in paracortical areas. In our case, histology of a cervical lymph node revealed follicular lymphoid hyperplasia with interfollicular infiltration by spindle-shaped mast cells with abundant, lightly staining cytoplasm. The presence of multifocal compact mast cell infiltrates or a diffuse compact mast cell infiltration pattern is highly compatible with the diagnosis of mastocytosis. However, in patients with the diffuse infiltration pattern, it is therefore impossible to establish the diagnosis of mastocytosis without additional studies, including the demonstration of an aberrant immunophenotype and/or detection of an activating point mutation in KIT. In the present case, a core biopsy on the cervical lymph node was nondiagnostic, due to prominent eosinophils, which obscure the mast cells infiltrate. Subsequently, lymphadenectomy showed densely packed, spindled mast cells aggregate predominantly in the parafollicular area, which confirmed the diagnosis of mastocytosis. Four patients with ASM with a presentation similar to the one described in this article were previously reported in the literature. In one patient KIT mutation status was not determined[2], and the other three patients were positive for KITD816V [3–5].

Previous studies have reported GI tract involvement by mastocytosis in small numbers of patients [6–8]. Histologically, involved GI endoscopic biopsy contained scattered single mast cells with expression of both CD117 and CD25, determined to represent minimal involvement by mastocytosis. Due to involvement was very focal and subtle in our case, the diagnosis of mastocytosis in mucosal biopsies was very difficult. The present case was initially diagnosed as chronic gastritis on the basis of the low dense of mast cells, and did not have endoscopic abnormalities, which added to the difficulty of diagnosis. Following recognition of mastocytosis in the lymphadenectomy, described above, the gastric biopsies were retrospectively stained for c-kit, revealing only a few scattered mast cells in the lamina propria, confirming SM in the stomach. The histologic differential diagnosis of mastocytosis in the GI tract is with reactive mast cell hyperplasia. Normal/reactive mast cells are usually loosely scattered throughout the sample and display round to oval nuclei with clumped chromatin, a low nuclear: cytoplasmic ratio, and absent or indistinct nucleoli. They are often appeared in normal mucosa or slightly increased in parasitic infection but do not show coexpression of CD117 and CD25, which can help in the differential diagnosis with mastocytosis.

Immunohistochemically, the CD117 positive mast cells with co-expression of CD2 and / or CD 25 is a sensitive and specific marker in the diagnosis of SM. Compared with normal mast cells, neoplastic mast cells abnormally express CD2 and CD25, but did not express most T or B antigens. Other markers including CD30, CD45, and CD68 are variably positive. In our case, the neoplastic mast cells mainly express CD117 and CD25, aberrant expression of CD2 is not seen in neoplastic mast cells, which is mainly expressed normally on some T lymphocytes. Prior studies have shown an association between CD30/123 expression and advanced disease [9–11], but data on this association is not particularly robust. We did not find CD30 or CD123 expression by neoplastic mast cells in our case.

Most cases of ASM harbor the KIT D816V mutation. The KIT gene, also known as CD117, encodes the KIT proto-oncogene receptor tyrosine kinase (c-KIT), a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRA, PDGFRB, CSF1R, FLT1, FLT3, FLT4 and KDR[12, 13]. KIT is a receptor for stem cell factor, important in regulating growth and development of hematopoietic cells[14]. The KIT gene is flanked by the PDGFRA and KDR genes on chromosome 4q12. Ligand binding to KIT results in kinase activation and stimulation of downstream pathways including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways promoting cell proliferation and survival[15]. A common kinase domain mutation that causes ligand-independent constitutive activation, D816V, occurs in 80–93% of aggressive forms of mastocytosis [16, 17]. In our case, some other genetic abnormalities were detected by NGS technology in addition to the KIT mutation, including ARID1A, BARD1, MYD88, TET2, KMT2C, POLE and RNF43 mutations, MSI-H and low tumor mutation burden. TET2 mutation is more frequently identified in SM with an associated haematological neoplasm. To the best of our knowledge, this is the first case of ASM reporting these genes abnormality. The relationship between ASM and these genetic abnormalities has not been documented thus far, so a large number of samples are needed to verify the relationship between ASM and these gene abnormalities.

Rapidly, the patient suffered from tumor dissemination, and finally died from respiratory failure almost 2 months after initial presentation. Several parameters have been described to be associated with an unfavorable prognosis in SM, including an absence of skin lesions, huge osteolyses, weight loss, malabsorption, enlarged liver with portal hypertension, and splenomegaly with hypersplenism[18–21]. In the present patient, absence of skin lesions, multiple bone lesions, weight loss, malabsorption and splenomegaly were observed. In a previous literature reported that lymphadenopathic mastocytosis with eosinophilia” was described as a separate, clinically aggressive variant of ASM[22]. There are also other cases of SM presenting with lymphadenopathy and eosinophilia exhibited a less aggressive course [3, 23]. Lymph node involvement with significant lymphadenopathy is extremely rare; when involved, it can mimic malignant lymphoma, creating a diagnostic challenge.

Conclusion

In conclusion, the diagnosis of ASM is frequently delayed due to the non-specific nature of symptoms and clinical presentations, as exemplified by our case with a lymphoma-like presentation. Diagnosis is difficult even if a patient shows symptoms of aggressive disease, lymphadenopathy, anemia, splenomegaly, and mild ascites. Herein, we present an unusual case of ASM with CD25 and CD117 expression and KIT mutations, with an aggressive clinical course and poor prognosis. Anyway, additional immunohistochemical and molecular studies are strongly recommended even in all suspected cases.

Abbreviations

ASM: Aggressive systemic mastocytosis ; SM: systemic mastocytosis; FDG-PET: Fluorine-18 fluorodeoxyglucose-enhanced positron emission tomography ; MSI-H :microsatellite instability high; GI :Gastrointestinal; CT :Computed tomography

Declarations

Acknowledgements

None.

Authors' contributions

Both authors performed the histological and immunohistochemical evaluation as well as collected clinical data and drafted the manuscript. Both authors read and approved the final manuscript.

Funding

This work was supported by the Outstanding Clinical Discipline Project of Shanghai Pudong (No. PWYgy2018-02)

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

This case study was approved by the Institutional Review Board for ethical committee of Tongji University Shanghai East Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Systemic mastocytosis involving cervical lymph node. (a) Hematoxylin and eosin stained section of the cervical lymph node with intact nodal architecture and numerous lymphoid follicles with prominent germinal centers. Mast cells arranged in tight clusters as well as singly are noted in the interfollicular areas. (b) A close-up of the spindle cell clusters with numerous ovoid to spindle nuclei and abundant clear cytoplasm. (c) Higher power shows increased number of primarily spindle-shaped mast cells admixed with eosinophils. Immunohistochemical stains reveal mast cells are strongly and diffusely positive for CD117 (d), CD25 (e) and negative for CD2 (f). A very subtle single aggregate of mast cells in the mucosa of the stomach was the only evidence of involvement in biopsies. The mast cells show expression of KIT (g), and CD25 (h). Mutation analysis of c-KIT identified D816V mutation in exon 17 (i).

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