

## CASE REPORT

# Cardiac complications in a patient affected by systemic mastocytosis and primitive myelofibrosis: A case report

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## Abstract

Systemic mastocytosis with associated primitive myelofibrosis is a rare and complex disease with a difficult therapeutic management. The release of several inflammation mediators can trigger acute cardiovascular events.

## KEYWORDS

acute coronary events, myeloproliferative neoplasm, systemic mastocytosis

## 1 | INTRODUCTION

Systemic mastocytosis is a rare and complex disease with important clinical manifestations related to the clonal proliferation of the mast. The associated primitive myelofibrosis significantly worsens the clinical scenario and the therapeutic approach and acute cardiovascular events can be triggered by the release of inflammation mediators.

Mastocytosis is a myeloproliferative neoplasm characterized by the clonal, neoplastic proliferation of morphologically and immunophenotypically abnormal mast cells (MC) that accumulate in one or more organ systems.<sup>1,2</sup> According to the last WHO classification,<sup>3,4</sup> mastocytosis is categorized into cutaneous (CM), systemic (SM), and mast cell sarcoma (MCS). The systemic mastocytosis diseases can be indolent, smoldering, with an associated hematological neoplasm (SM-AHNMD), aggressive, and mast cell leukemia.<sup>3</sup>

The clinical manifestation of the mastocytosis is variable, depending on the particular sub-type.

Symptoms of systemic mastocytosis can be chronic or episodic and are often triggered by exogenous and endogenous causes<sup>2,5</sup> (cold/heat, physical exertion, insect venoms, alcohol, infections, emotional stress).

An increase of risk of anaphylaxis seems to be common to all the different variants.<sup>2</sup>

Common symptoms include facial flushing, pruritus, palpitations, dizziness, hypotension, syncope, breathing difficulties, abdominal pain, nausea, vomiting, diarrhea, headache, sweating, lethargy, fatigue, arthralgia and myalgia, lack of concentration, irritability, anxiety, and depression.<sup>5</sup> Remarkable, skin findings are rare in SM and the absence correlates with the aggressiveness of the disease.<sup>2,6</sup>

In patients with SM-AHNMD, it may be difficult to attribute symptoms to mastocytosis as they may have signs

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and symptoms related to the associated hematological disorder.<sup>7,8</sup>

The increase of risk of solid cancers as well as cardiovascular diseases associated with SM-AHNMD has been considered by some authors,<sup>8,9</sup> and it was pointed out the higher rate to develop cardiovascular complications.

In particular, a higher frequency of thromboembolic events was associated with patients affected by the Jak2V617F mutation than without.<sup>10</sup>

Treatment of patients with SM-AHNMD depends on the associated hematologic condition.

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm characterized by stem cell-derived clonal myeloproliferation, abnormal cytokine expression, bone marrow fibrosis, extramedullary hematopoiesis, constitutional symptoms, cachexia, leukemic progression, and shortened survival.<sup>1</sup>

Diagnosis is based on bone marrow morphology. The presence of fibrosis, JAK2/MPL mutation, or 19/13q2 cytogenetic abnormality is supportive but not essential for diagnosis.

The main clinical manifestations in PMF involve anemia, marked hepatosplenomegaly, constitutional symptoms (eg, fatigue, night sweats, and fever), cachexia, bone pain, splenic infarct, pruritus, thrombosis, and bleeding. Ineffective erythropoiesis and extramedullary are the main causes of anemia and organomegaly, respectively.

The pathogenesis of myelofibrosis is not completely understood, but the dysregulation of Janus kinase (JAK)-signal transducers and activators of transcription (STAT) are involved.

Both JAK1 and JAK2 signaling appear to be involved, whereas overactivation of JAK2 is associated with malignant myeloproliferation, and dysregulation of JAK1 signaling is linked to inflammatory symptoms. About 50% of patients affected by myelofibrosis present the JAK2V617F mutation, associated with overactivation of the JAK-STAT pathway.<sup>11</sup>

Compared with other SM-AHN, SM with associated PMF is relatively rare, likely because it can be missed as a result of dry tap and/or fibrosis.<sup>12</sup>

At the moment, the only drug therapy, specifically approved in the USA for the treatment of patients with intermediate- or high-risk myelofibrosis, and in the EU for the treatment of disease-related splenomegaly or symptoms in patients with myelofibrosis, is the selective inhibitor of JAK1 and 2 ruxolitinib.

The efficacy of the drug was evaluated in two comparative trials<sup>13</sup> (COMFORT-I and -II) that reported an improvement of general symptoms and health-related quality-of-life scores. In particular, compared with best available therapy, ruxolitinib was associated with reduction of splenomegaly and other disease-related

symptoms,<sup>14</sup> though overall survival impact is not proved yet.

Hematological and non-hematological adverse events related to therapy with ruxolitinib have been described.<sup>11,14</sup> Thrombocytopenia and anemia are typical events, also related to the mechanism of action of the drug, but they are dose related and unfrequently led to the interruption of the therapy and did not unfavorably affect the survival effect related treatment. These events are usually managed with dose reduction and/or transfusion of packed red cells. The more frequent non-hematological adverse events are represented by bruising, dizziness, and headache (grade 1 or 2 in severity) while the most common grade 3 or 4 were abdominal pain, diarrhea, constipation, vomiting, fatigue, and dyspnea.

The more recent drug approved for the SM-AHNMD is midostaurin, a multitarget inhibitor active against KIT D816V mutation, approved in 2017 by FDA and EMA after two open label II phase studies.<sup>15</sup> The most frequent adverse events observed were low-grade nausea, vomiting, and diarrhea while new or worsening hematological abnormalities (grade 3 or 4 neutropenia, anemia, and thrombocytopenia) were observed in different percentages (from 24% to 41%), mostly in patients with already present anomalies.<sup>16,17</sup>

## 2 | CASE REPORT

A 43-year-old Caucasian male was referred to the Emergency Department of the Polyclinic Hospital “Umberto I” of Rome, with a worsening asthenia and dyspnea in the past days.

The medical history reports a trauma 5 years before with hip fracture and splenectomy.

A systemic mastocytosis (SM) with an associated primitive myelofibrosis was diagnosed two months before with Jak2V617F and c-kit D816V mutations.

A tobacco smoking habit completes the medical history.

At the admission time, the patient was under treatment, in the Hematological center of the same Hospital, with midostaurin and ruxolitinib. The patient assumed also furosemide, allopurinol, and pantoprazole.

The physical examination revealed a marked hepatomegaly with extension of the liver down to the right iliac fossa and to the left flank.

The routine laboratory analyses revealed several disorders, as shown in Table 1.

Noticeable was the reduction observed in red cell count ( $2.77 \times 10^6/\mu\text{l}$ ), hemoglobin (9 g/dl), platelet count ( $60 \times 10^3/\mu\text{l}$ ), and the increase in white cell count ( $14,78 \times 10^3/\mu\text{l}$ , with  $10.35 \times 10^3/\mu\text{l}$  neutrophils and  $1.94 \times 10^3/\mu\text{l}$  monocytes).

**TABLE 1** Main laboratory analyses values at admittance

	Values at admission	Normal range
Red cell count*	$2.77 \times 10^6/\mu\text{l}$	$(4.3\text{--}5.9) \times 10^6/\mu\text{l}$
Hemoglobin*	9 g/dl	13–17 g/dl
Hematocrit*	28.7%	40–52%
Mean cell volume*	103.4 fl/red cell	80–96 fl
Mean cell hemoglobin	35.2 pg/red cell	27–33 pg/red cell
Mean cell hemoglobin concentration	34 g/dl	32–36 g/dl
Red cell distribution width	20.4%	11–16%
White cell count*	$14.78 \times 10^3/\mu\text{l}$	$(4\text{--}10) \times 10^3/\mu\text{l}$
Neutrophils*	$10.35 \times 10^3/\mu\text{l}$	$(2.2\text{--}6.6) \times 10^3/\mu\text{l}$
Lymphocytes	$1.68 \times 10^3/\mu\text{l}$	$(1\text{--}3.2) \times 10^3/\mu\text{l}$
Monocytes*	$1.94 \times 10^3/\mu\text{l}$	$(0.2\text{--}1) \times 10^3/\mu\text{l}$
Eosinophils	$0.04 \times 10^3/\mu\text{l}$	$(0\text{--}0.8) \times 10^3/\mu\text{l}$
Basophils	$0.06 \times 10^3/\mu\text{l}$	$(0\text{--}1.5) \times 10^3/\mu\text{l}$
Platelet count*	$60 \times 10^3/\mu\text{l}$	$(150\text{--}450) \times 10^3/\mu\text{l}$
Reactive C-protein	13.37 mg/dl	0–0.5 mg/dl
Tryptase*	>200 $\mu\text{g/L}$	<11.4 $\mu\text{g/L}$
HS Troponin T*	0.018 $\mu\text{g/L}$	< 0.014 $\mu\text{g/L}$
Creatinine*	2.7 mg/dl	0.1–1.2 mg/dl

\*Altered value is marked with asterisk.

To note the high tryptase level (>200  $\mu\text{g/L}$ , where normal value is <11.4  $\mu\text{g/L}$ ) obtained both at admittance time and after the cardiac ischemic event (see later).

The blood gas analysis reported pH = 7.44,  $\text{pCO}_2$  = 27 mmHg,  $\text{pO}_2$  = 64 mmHg,  $\text{SpO}_2$  = 93.4% and  $\text{H}_2\text{CO}_3^-$  = 18.3 mmol/L, with  $\text{FiO}_2$  = 21%.

The  $\text{FiO}_2$  was increased to 40%, and an echocardiogram was carried out that evidenced a large and severe circumferential pericardial effusion (maximum values 25 mm in the inferoposterior and 23 mm close to the right ventricle in the parasternal short axis) with an incipient collapse of the upper wall of the right atrium. The remaining examination is almost normal with conserved systolic function and ejection fraction.

It was decided to proceed with an echo-guided pericardiocentesis to an expeditious removal of a total of 500 cc serosanguineous fluid from the pericardial space. At the end of the surgical procedure, a chest tube was placed in the pericardial space.

The pericardial fluid was cytologically analyzed and the cell characteristics confirmed the known pathologies.

Both midostaurin and ruxolitinib were interrupted.

Contrast chest and abdominal multislice CT were performed the next day and showed a residual effusion flap as well as the correct placement of the drainage chest tube. CT showed a large subcapsular hematoma (15 × 6.2 × 13 cm), of the left liver lobe, with areas of

mixed densities suggestive of a recent hemorrhage (see Figure 1A,B) and was interpreted as a complication of the surgical procedure.

The image analysis showed addition remarkable items: A fair amount of bilateral pleural effusion (most evident on the left lungs), with atelectasis of the postero-basal segments of the lower lobes of both lungs.

Several lymphadenopathies in the axillar, and supraclavicular regions, as well as at the mediastinum were detected.

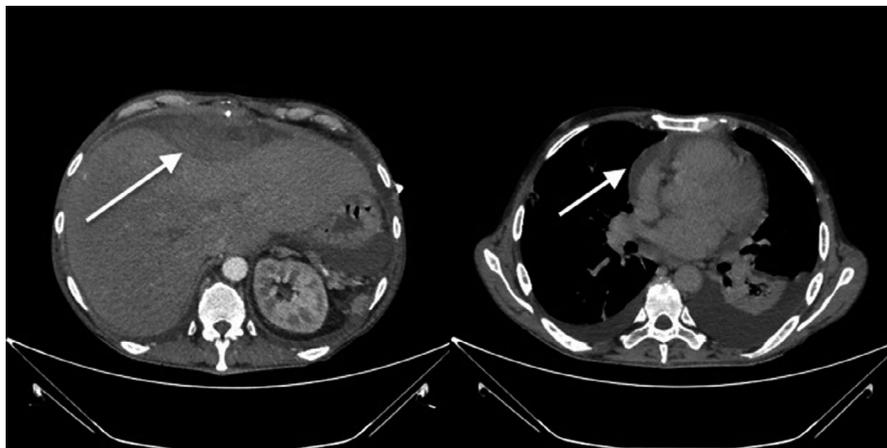
It is worthwhile to observe that the diffuse lymphadenopathies were already observed in a previous CT carried out three months before.

An electrocardiogram (ECG) control carried out in the same day, revealed a prolongation of the QTc interval to a value of 549 ms (Figure 2A). Except for a slight delay for the intraventricular conduction (QRS = 10.5 ms), the other features of the ECG were normal.

The second day after the surgical procedure, additional 150 cc of serosanguineous fluid was removed by the drainage chest tube and the QTc value, at the ECG control, reduced to 490 ms.

The fifth day a control echocardiogram revealed a normal pericardial condition.

The recovery course proceeded for other three days, where the serial ECG checks for the QTc values displayed a constant reduction toward the normal range.



**FIGURE 1** Computed tomography. Left: Large intraparenchymal hematoma located at the left liver lobe, with a hyperdense amount of blood as for recent bleeding. Right: Fair amount of pericardial

The ninth day the patient had a sudden chest pain and the recorded ECG showed ST changes of ischemic meaning on multiple leads (Figure 2B). Nitrates were administered and after 5 min the patient referred the disappearing of the chest pain and a second ECG, repeated after 30 min since the chest pain onset, did not show ST changes. T waves inversion was still present in the anterior precordial leads (Figure 2C).

The case was discussed with the cardiologists of the cath laboratory, but, in view of the clinical conditions and, in particular, of the recent hepatic bleeding, it was decided to supersede the coronary angiography procedure and to monitor the patients.

The next day (10th) the ECG almost normalized (Figure 2D). The complete ECG sequence together with the clinical scenario suggested a coronary spastic angina event.

After 18 days of hospitalization, the patient was discharged and referred to the hematological center to re-evaluate the specific therapy.

### 3 | DISCUSSION

We present here an interesting clinical case of cardiac complications in a patient affected by systemic mastocytosis with primary myelofibrosis.

Firstly, the patient reported a severe pericardial effusion, with a drainage procedure complicated with an intraparenchymal hemorrhage caused by the presence of a marked extension of the enlarged liver. Some days after this event, when the pericardial effusion was almost resolved, the patient experienced an episode of coronary spastic angina.

It is well known that patients suffering of myeloproliferative neoplasms<sup>9,10,18</sup> have an increased risk of cardiovascular diseases, but only few analyses have been reported when systemic mastocytosis is considered.<sup>19,20</sup>

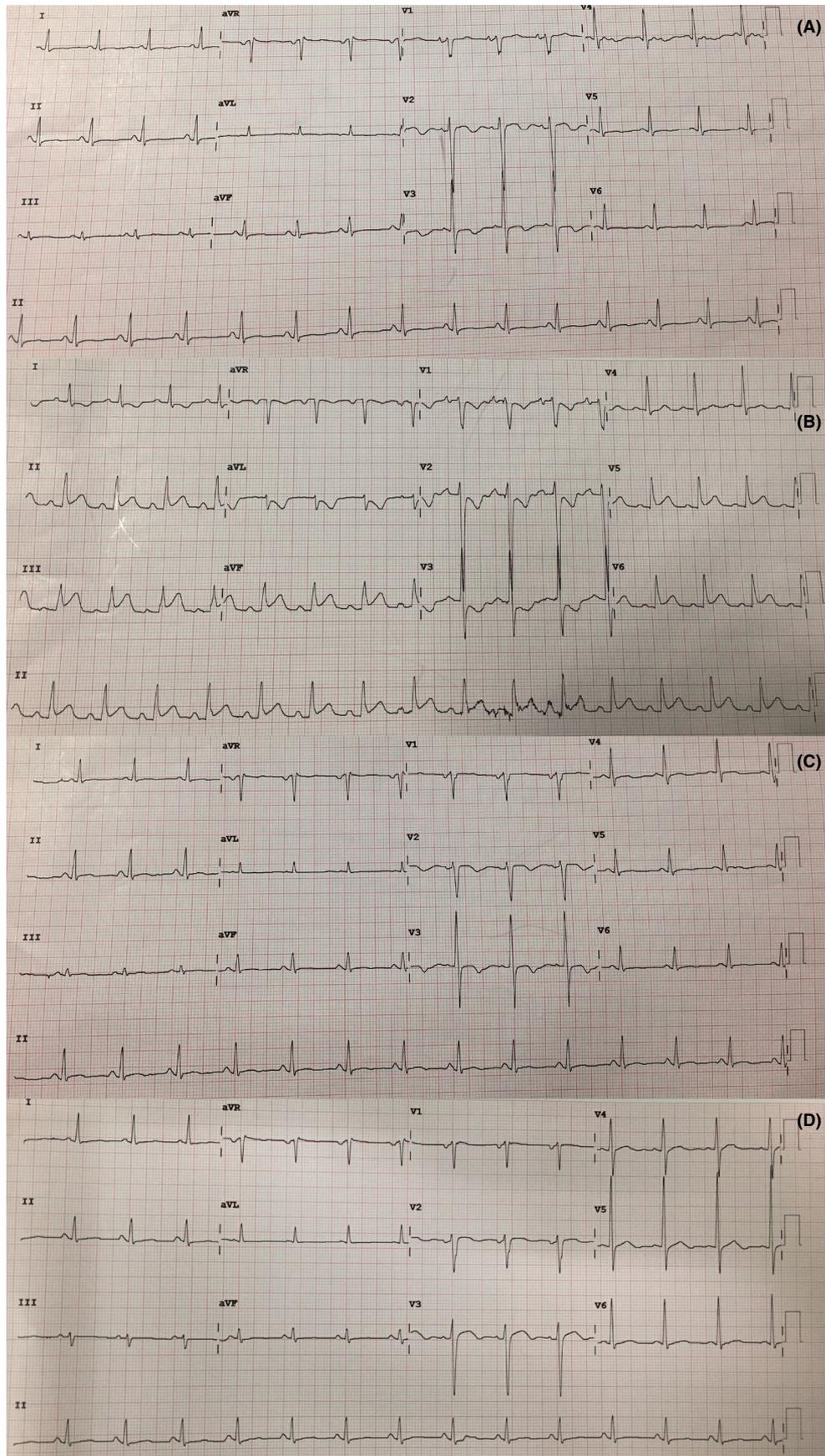
Triggers of pericardial effusion can be divided in inflammatory and non-inflammatory.<sup>21</sup> The first group is related to infectious, autoimmune, drug-linked causes, while in the second area the most frequent triggers are neoplastic, metabolic, traumatic, or cardiovascular diseases. In particular, hematological neoplasm in presence of thrombocytopenia is a significant risk factor.<sup>22</sup>

Moreover, myelofibrosis is frequently characterized by extramedullary hematopoiesis in spleen and liver and a rapid increase on liver size has been observed in patients after splenectomy,<sup>23</sup> like in the present case. Pericardial effusion related to extramedullary hematopoiesis has been described in few occasions and the pathophysiological mechanism is not completely understood though it seems related to the increased vascular permeability.<sup>23,24</sup> In the case here presented, the microscopic examination of epicardial or pericardial tissue was not carried out so the association of pericardial effusion to extramedullary hematopoiesis cannot be confirmed, although highly probable.

Furthermore, the mastocytosis is an additional risk factor for cardiac complications for this patient and the severe pericardial effusion could also be induced by the inflammatory response of activation of mast cells<sup>25</sup> typical of this disease.<sup>19</sup> In fact, mast cells are abundant in heart tissue, in particular close to coronary vessels and are involved in atherosclerosis, cardiac diseases, Kounis syndrome.<sup>19,20,26,27</sup>

The observed coronary spastic angina event is likely to be related to mast cells mediators<sup>28</sup> (histamine, TNF- $\alpha$  and platelet-activating factor, in particular) that can induce vasospasm of coronary arteries.

Since 1991, the coronary artery spasm occurring in the context of an anaphylactic reaction is considered one of the possible clinical manifestation of Kounis syndrome, which actually is defined as the occurrence of acute coronary syndromes (coronary spasm, acute myocardial infarction, stent thrombosis) in conditions related to mast cell and platelet activation.<sup>26,29</sup>



**FIGURE 2** ECG sequence. A, ECG recorded immediately the post pericardiocentesis procedure. B, ECG recorded at the onset of the chest pain. C, ECG recorded 30' after the onset of chest pain. D, ECG recorded the day after the spastic coronary event

The event described fits the characteristics of Kounistype presentations, in fact, high levels of tryptase, as those detected in this case report, have been shown to be related to mast cell disorder. In particular, the values measured both at admittance and the day after the coronary vasospastic event, were much higher (over the 200 µg/L, laboratory limit) than the value considered to be normal (11.4 µg/L). These values are suggestive of possible cardiac emergencies and should be monitored for this class of patients.<sup>30,31</sup>

In conclusion, this case report presents the possible cardiac complications of the quite rare systemic mastocytosis associated with the hematological neoplasm (SM-AHNMD) and highlights the difficulty of the clinical management.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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None.

## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

All authors contributed to the design of this manuscript. MS and LM wrote the first draft. LM, PP, and GM wrote the final manuscript. GM and RG scientifically reviewed the manuscript.

## CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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