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Case Report

Extramedullary hematopoiesis causing spinal cord compression in polycythemia vera: A case report and literature review

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ABSTRACT

Extramedullary hematopoiesis (EMH) is a rare cause of spinal cord compression defined as finding hematopoietic elements outside the physiological location in the bone marrow. We report the case of a 70-year-old man with JAK 2 positive myeloproliferative syndrome type polycythemia vera (PV), initially treated with hydroxyurea. Two years after diagnosis, he presented progression with biological and clinical evolution associating hyperleukocytosis and hepatosplenomegaly with no evidence of acute myeloid leukemia. Treatment with hydroxyurea and ruxolitinib was introduced. Six months later, clinical symptoms suggesting spinal cord compression from the T2 region appeared. Medullary MRI revealed a multistage spinal cord injury from T2 to S1, while brain CT excluded any intracranial location. The biopsy diagnosed extramedullary hematopoiesis with no CD34 + blast cell, corresponding polycythemia vera. Given the lack of consensus and after a review of the literature, irradiation was planned to treat a volume from T1 to S2 with a dose of 18 Gy in 10 sessions of 1.8 Gy. At the end of the radiotherapy, the patient started to recover his motor and sensory functions. Six months later, he walked without assistance and had no significant acute toxicity. Using radiotherapy to treat spinal cord compression caused by EMH is justified with excellent early response and no major side effects. We present here this case and the systematic review of the literature on this matter.

Case presentation

A 68-year-old man was initially diagnosed with a JAK 2 positive myeloproliferative syndrome of the polycythemia vera (PV) type. The initial hematocrit was 62.5 %, leukocytes 7960 per mm³, endogenous EPO was normal at 7.2, myeloma at 1.5 %. Treatment with hydroxyurea and bloodletting was initiated allowing a partial response. Two years later, clinical and biological evolution was observed. There was abdominal pain with hepatosplenomegaly, hyperleukocytosis of 70,590 per mm³, myelocytes at 0.8 %, platelets 296,000 per mm³, hematocrit was normal at 49.5 %, as was hemoglobin at 13.1 g/dl. The myelogram showed erythroblastosis at 40 %, and the osteomedullary biopsy revealed myeloproliferative neoplasia compatible with polycythemia vera with no excess of CD34 + blasts. A second line of treatment with hydroxyurea and ruxolitinib was introduced. Six months later, the patient presented with low back pain and a walking deficit. Clinical

examination suggested spinal cord compression, with a sensory level beginning at T10, evidence of both upper and lower motor neuron weakness, flexor deficiency, especially at the L2 level, and vegetative dysfunction with urinary and erectile dysfunction. A CT scan and MRI revealed bilateral paravertebral masses staggered along the spine from T2 to S1, suggesting extramedullary hematopoietic lesions with a hyperintense mass on T2 and isointense with peripheral enhancement on T1 (Fig. 1). A biopsy of the right thoracic paravertebral mass confirmed the focus of extramedullary hematopoiesis with no CD34 + blast cells.

After a review of the existing literature (Table 1), the decision was made to irradiate the patient without previous surgery.

Radiotherapy was performed after computed tomography images were acquired and fusion with the diagnostic MRI to define the clinical target volume (CTV) corresponding to the spinal canal from T1 to S2. The planned target volume (PTV) was obtained using a 20 mm 3D

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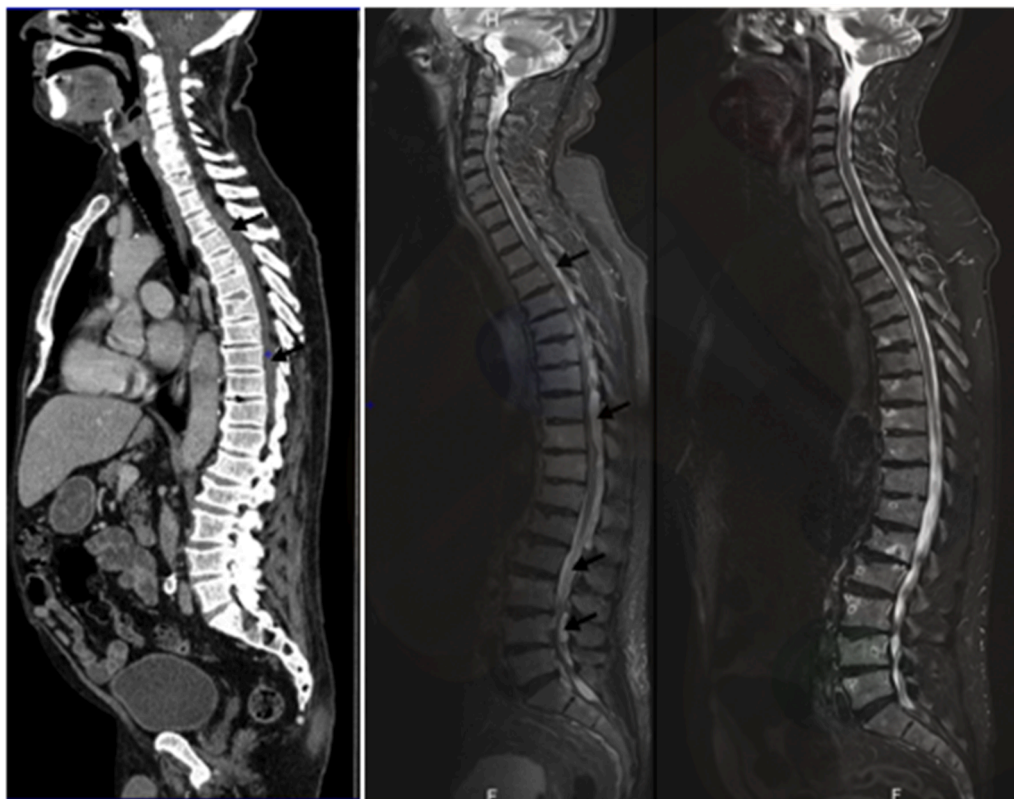


Fig. 1. Extramedullary hematopoiesis in the spinal canal with compression of the spinal cord and the terminal filum. Sagittal view injected CT scan (left) and MRI STIR sequence before RT (middle) and three months after RT (right).

Table 1

Literature review of cases with extramedullary hematopoiesis causing spinal cord compression and polycythemia vera.

Year	Sex	Age	Symptoms	Localization	Treatment	Neurological symptoms/ survival	Imagery	Reference
1980	Man	68	Paraplegia Pain	T4-T8	Laminectomy Corticosteroids 9 Gy /3F	No improvement at 6 months/NA	Radiography	Rice [1]
1989	Man	52	Quadriplegia Pain	C4	15 Gy/1F	No improvement until his death 15 days later	Myelography	Jackson [2]
1989	Man	46	Paraplegia	T4-T6	Laminectomy	NA/Died	CT-scan	de Morais [3]
2002	Woman	69	Paraplegia	T4-T9	Laminectomy 20 Gy in 14d	CR	MRI	Ohta [4]
2001	Man	40	Paraparesis	T10-T12	Laminectomy	CR/Lost of follow-up	MRI	Rutherford [5]
2003	Man	30	Pain/loss of sensitivity	T5-T10 L3-S1	Lumbar Laminectomy 16 Gy/8F T6-L3 Corticosteroids	No improvement after laminectomy Partial remission after radiotherapy*	MRI	Masmas [6]
2004	Man	43	Paraplegia	T3-T11	Laminectomy	CR	MRI	Piccaluga [7]
2008	Man	72	Paraparesis	T3-T12	Laminectomy Radiation therapy	NA	MRI	Baehring [8]
2015	Man	69	NA	C6-Coccyx	Hydrea not efficient 30.6 Gy/17F craniospinal	CR	MRI	Scott [9]
2011	Woman	67	Seizure	Cranial	Surgery Radiation therapy	CR	Head CT-Scan	Zherebitskiy [10]
2011	Man	68	NA	T4-T8	Laminectomy	Near complete functional recovery	MRI	Zherebitskiy [10]
2013	Woman	23	Pain	C2-C3	25 Gy/10F	CR	MRI	Mattei [11]
2017	Man	55	Paraparesis	T5-T10	Surgery	CR	MRI	Ito [12]
2020	Man	72	NA	T8-T12	30 Gy/15F	CR 10 days after RT 3 years later: Recurrence above the radiation fields: Second remission with 30 Gy/15F	MRI	Fontanesi [13]

CR = Complete response; CT scan: computed tomography; MRI: Magnetic resonance imaging; NA: not available; RT: Radiotherapy.

*: Following laminectomy: progressive cauda equine syndrome with reduced muscle strength in the left leg, reduced sensibility in the anogenital region and distal to the left knee, retention of urine, and reduced contraction of the anal sphincter. A new MRI did not demonstrate intraspinal hematoma. Radiotherapy was initiated and the patient experienced regression of the symptoms: nearly normal muscle strength and sensibility in the legs but still suffered from mild retention of urine and sexual impotence. The MRI also showed regression.

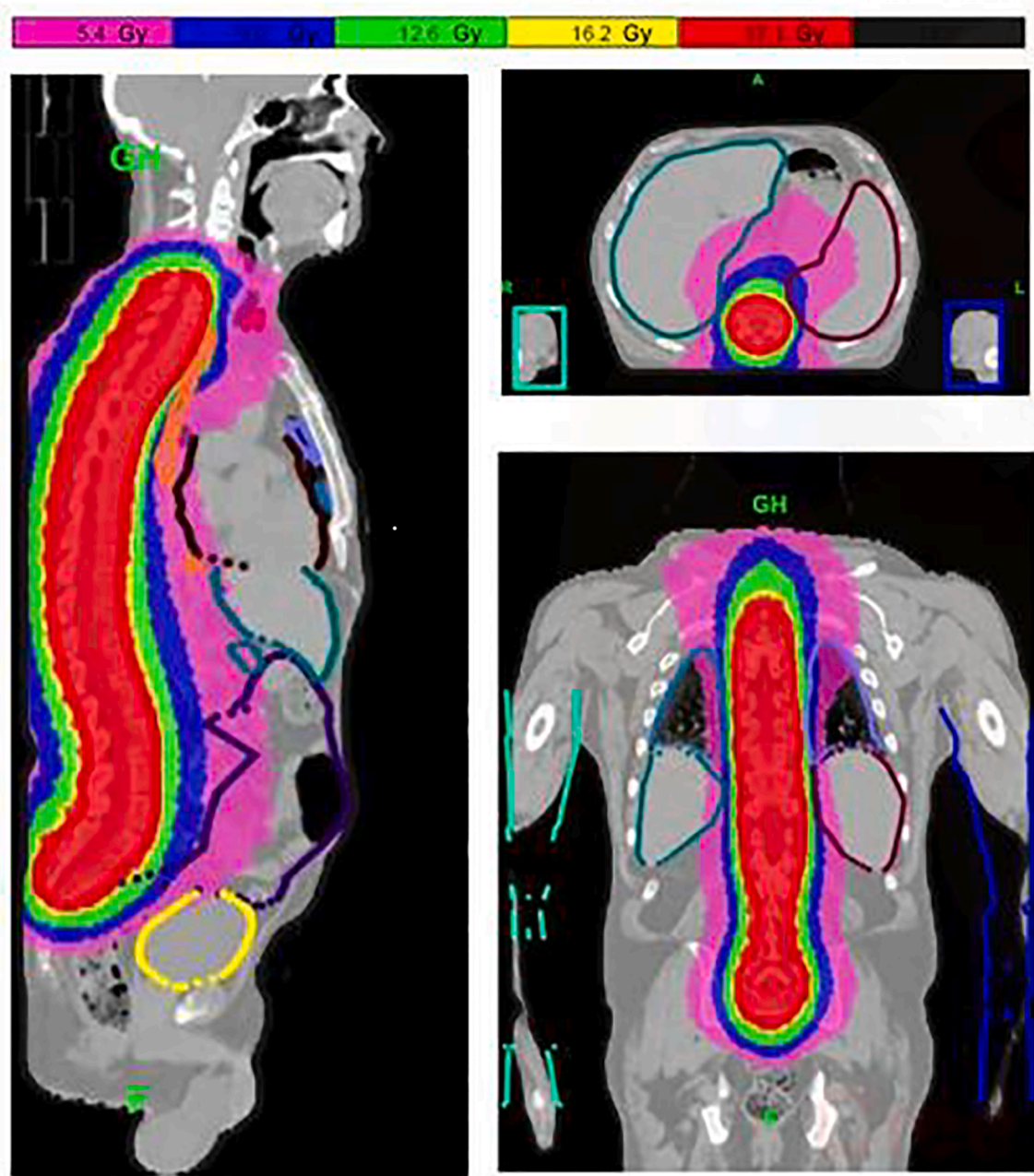


Fig. 2. Radiation therapy planning. Isodose distribution in color wash, scale above.

Table 2
Motor function evaluation before, during and after the radiotherapy.

Testing	Before RT		End of RT		1 month post-RT		3 and 6 months post-RT	
	Right	Left	Right	Left	Right	Left	Right	Left
	L2	0	0	5	2	5	4	5
L3	3	3	5	4	5	5	5	5
L4	3	3	5	4	5	5	5	5
L5	5	4	5	5	5	5	5	5
S1	5	4	5	5	5	5	5	5

geometric expansion from the CTV. Treatment planning was carried out with a tomotherapy dedicated inverse treatment planning system. We prescribed 18 Gy in 10 fractions of 1.8 Gy, five days per week, using helical Tomotherapy (6 MV photon beams). (Fig. 2).

At the end of the radiotherapy, the patient started to recover his motor and sensory functions. One month later, he was walking without assistance, strength recovery was almost complete (4/5 strength scale on the left flexor) (Table 2), almost resolved erectile dysfunction and no significant acute toxicity. Three months later, the patient had totally recovered his strength, and there remained only discrete paresthesia in the plantar area of the feet. At 3 months, the MRI showed a very significant decrease in paravertebral masses and in the thoracic spinal canal, with the total disappearance of the lumbosacral masses and the development of small lesions in the T2 hypersignal osteomedullary lesions of the thoracolumbar spine and sacrum that were both asymptomatic and non-specific. (Fig. 1, middle and right). MRI confirmed complete response at 6 months.

Discussion

Extramedullary hematopoiesis (EMH) is often defined as the production of mature erythroid and myeloid progenitor cells outside the bone marrow. This condition can occur in almost any disease that results in bone marrow infiltration or inefficient hematopoiesis, such as infectious diseases [14] and solid malignancies [15]. It is often a complication of myeloproliferative neoplasms [16], including polycythemia vera (PV). PV can present many complications, including EMH, which can occur at any stage of the disease [17]. Other complications can be a transformation into myelofibrosis or acute leukemia with a poor prognosis.

EMH can occur in the thoracic paravertebral region but mostly in the liver and spleen [18]. The spleen is palpable in more than one-third of patients with PV [19]. This can lead to abdominal pain and, in some cases, portal hypertension. Complications of concern are often most notable when EMH occurs near the central nervous system, which can lead to spinal cord compression [20].

This may be explained by the fact that the liver is the first site of children's hematopoietic stem cell (HSC) differentiation. These cells then rapidly differentiate in the spleen before becoming intramedullary hematopoietic cells during embryogenesis [14]. HSCs must be in an appropriate microenvironment to differentiate; thus, the EMH must contain HSCs. The EMH must thus contain HSCs and an alternatively feasible niche for cell maturation. The role of a number of chemokines, cytokines, and growth factors, based on their established roles in hematopoiesis, should be investigated for their role in EMH [21].

The treatment of EMH-induced spinal cord compression is not consensual. Surgical decompression alone or combined with post-operative radiation has been reported, as has the use of radiation alone and systemic therapies [11]. The radiosensitivity of hematopoietic lineages explains that low-dose radiation has been found to achieve high rates of local remission [22].

The dose schedule chosen for this patient was in line with the literature and in parallel with the treatment of splenomegaly related to this pathology, i.e. 18 Gy delivered in 10 fractions of 1.8 Gy [23]. Thus, we suggest using 16 to 20 Gy with a classical fractionation regimen (1.8 to 2 Gy). Indeed, lower doses do not seem to lead to a sufficient improvement in symptoms [1], and the regimen using a single fraction of 15 Gy did not benefit the patient [2]. Increasing the dose beyond 20 Gy does not appear to provide additional benefit; the responses of patients treated at lower doses, like our patient, persist over time. For the CTV, there is no consensus in the literature. However, a recurrence above the irradiation fields has been observed, suggesting the benefit of irradiating at least one vertebra above and one vertebra below the lesion. For the PTV, a CTV's expansion from 10 to 20 mm, like in the vertebral metastases' radiotherapy of solid tumours, is suitable.

In our case, the radiotherapy was highly effective, with a clinical effect from the end of the irradiation, which improved at 1 month and 3 months. MRI at 3 months showed total disappearance of the lumbosacral masses and a significant decrease in the medullary and extramedullary thoracic canal masses. The response is stable over time and confirmed by MRI at 6 months.

In a retrospective analysis [22], the spine was the most common location studied for non-hepatosplenic EMH. Radiation therapy was undertaken in 7 patients, 5 of whom achieved complete resolution of their symptoms, suggesting that either option may be beneficial. Our own experience suggests that radiation therapy alone may be efficient in patients with extended spinal cord compression caused by extramedullary hematopoiesis.

Conclusion

Our case confirms the data in the literature where radiotherapy alone is safe and effective in treating extramedullary hematopoiesis. The

significant motor deficit at diagnosis could have required emergency surgery, but radiotherapy allowed complete recovery.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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