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112.THALASSEMIA AND GLOBIN GENE REGULATION

Case Series of Paraspinal Extramedullary Hematopoiesis in Transfusion-Dependent Thalassemia Treated with Luspatercept

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Introduction: Extramedullary hematopoietic (EMH) pseudo-tumors are commonly seen in patients with non-transfusion dependent thalassemia but rare in transfusion-dependent beta thalassemia (TDT). Paraspinal EMH is more prevalent in older patients with severe ineffective erythropoiesis and low fetal hemoglobin levels. Luspatercept, an inhibitor of the TGF-beta pathway, has been shown to reduce transfusion requirements and improving iron overload in TDT. Emerging data report risk of EMH in patients receiving luspatercept, resulting in updated safety labeling, yet there is scarce data on the optimal management of EMH. In this case series, we present four cases of paraspinal EMH in TDT patients in their twenties treated with Luspatercept, and report management approaches and treatment response.
Methods: We conducted a retrospective analysis of adult patients with TDT receiving luspatercept in the Northern Alberta hemoglobinopathy program and identified those who developed EMH. Clinical, laboratory and imaging data were collected, including transfusion requirements, clinical presentation, management strategies, and response to treatment.
Results: From June 2021-June 2023, 9 patients with TDT received luspatercept therapy. Three discontinued therapy early, median 2 months (range 1-4), due to side effects (2 severe headache, 1 erratic Hb). Six patients (2F, 4M) continued for long term use. One had baseline MR spine, and 1 had small thoracic EMH noted on cardiac MR; 5/6 underwent MR spine post luspatercept therapy, 1 for neurologic symptoms, 4 for EMH screening.
We identified 4 cases of EMH. Luspatercept treatment median 17 months (range 14-20). All 4 patients were males, median age 24 years (range 20-29). All 4 patients had documented history of massive splenomegaly, 2 requiring splenectomy, 1 requiring partial splenic embolization. All 4 cases had significant elevations in reticulocyte count, nRBC, and 2/4 had thrombocytosis (Table 1).
Case 1 presented with progressive leg weakness with resultant hemiplegia. Cases 2 and 3 were asymptomatic and found on screening MRI. Case 4 had pre-existing, asymptomatic paraspinal EMH first noted 4 years prior, had enlarged prior to luspatercept, and then enlarged further on CT chest 16 months post luspatercept.
Treatment varied according to severity of EMH. Case 1 was hospitalized for 2 months, treated with 18 Gy radiation, dexamethasone for 2 months, hydroxyurea 2000 mg (24 mg/kg), hypertransfusion (goal Hb > 110 g/L) and luspatercept discontinuation. He regained mobility after therapy. Case 3 had impending spinal cord compression. Luspatercept was stopped, and he received radiation therapy 18 Gy, followed by hydroxyurea 1000 mg (16 mg/kg). Case 2, asymptomatic, continued luspatercept, hydroxyurea was added, with planned increased surveillance MR and physical examination. Case 4, initially asymptomatic, continued luspatercept, with increased transfusion threshold. Later he developed symptoms, luspatercept discontinued, and hydroxyurea initiated.
Discussion: Paraspinal EMH is uncommon in TDT. However, our case series highlights the occurrence of paraspinal EMH in younger TDT patients treated with luspatercept. All four patients were male, with risk factors for EMH including massive splenomegaly and brisk reticulocytosis.
Management options for paraspinal EMH include increased transfusions, hydroxyurea, radiotherapy, surgical decompression, or a combination thereof. Low-dose radiation has shown promising results although access in resource-limited settings and recurrence remain a concern.
Limitations of this review include the retrospective nature and small number of patients; a causal relationship cannot be established. Further, given the lack of prior surveillance MRI spine, it is not clear the exact timing of EMH development. Further studies are needed to establish the long-term efficacy and safety of luspatercept in patients with TDT.
Conclusion: Paraspinal EMH is a rare complication in TDT patients, but its occurrence should be considered, especially with the increasing use of luspatercept. Screening guidelines for EMH should be established to detect and manage this potentially

debilitating condition promptly. In the absence of guidelines, based on the high rate of EMH noted in our cohort, we propose screening MRI spine as a baseline prior to luspatercept, with consideration of regular surveillance MRI post therapy.

Disclosures Sun: *Takeda:* Honoraria; *Shire:* Honoraria; *Sobi:* Honoraria; *Sanofi:* Honoraria; *Pfizer:* Honoraria.

OffLabel Disclosure: Hydroxyurea use for extramedullary hematopoiesis

Table 1: Case summaries

Case	Age, gender	Median Pre-transfusion CBC/retic values	Liver/Spleen status	Luspatercept	Symptoms	Imaging	Management	Outcome
1	20 y/o, male	HB 81g/L Plt 639 10^{12}/L nRBC 355.8 Retic 265.7 10^{12}/L	Post splenectomy No hepatomegaly	1.25 mg/kg SC q 3 weeks, 30% reduction transfusion burden	Progressive leg weakness, hemiplegia	**14 months post luspatercept MR spine:** extensive epidural soft tissue enhancement from T2 to sacrum with **significant spinal cord compression**	Admission to hospital (acute care → rehab hospital) for 2 months Discontinue luspatercept Dexamethasone 4 mg QID, with 2 moth taper Radiation therapy 18 Gy Hydroxyurea 2000 mg (24 mg/kg) Hypertransfusion, goal Hb > 110 g/L	Regained mobility Repeat imaging pending
2	23 y/o, male	HB 88 g/L Plt 952 10^{12}/L nRBC 643.5 Retic 692.710^{12}/L	Post splenectomy No hepatomegaly	1.25 mg/kg SC q 3 weeks for 2 years, with a resultant 43% decrease in transfusion burden	Asymptomatic	**19 months post luspatercept MR spine:** small nodular focus consistent with extramedullary hematopoiesis is seen in the anterior epidural space at the L5 and S1 levels	Hydroxyurea (14 mg/kg) initiated Luspatercept continued Increased MR surveillance and physical examination	Remains asymptomatic
3	29 y/o, male	HB 91 g/L Plt 215 10^{12}/L nRBC 16.7 Retic 157.710^{12}/L	Splenomegaly 20 cm prior to splenic embolization (2018) Post splenic embolization spleen 14 cm prior to luspatercept initiation No hepatomegaly	1 mg/ kg SC every three weeks 46% reduction in transfusion requirements	Asymptomatic	**15 months post luspatercept MR spine:** multiple anterior paraspinal masses, most prominently in the thoracic and sacral region. Masses extend through the sacral vertebra and moderate narrowing of the canal and neural foramen of the sacrum. Small dorsal epidural lesions in the thoracic region, most prominent at T6-7, with mild **spinal canal narrowing** and **mild spinal cord displacement** but no convincing impingement	Luspatercept discontinued Radiation therapy (18Gy) due to impending spinal cord impingement. Hydroxyurea initiated (16 mg/kg) after radiation therapy to prevent recurrent EMH.	Remains asymptomatic Repeat imaging post radiation pending
4	24 y/o, male	HB 83g/L, Plt 189 10^{12}/L, nRBC 5.7 Retic 189.510^{12}/L	Splenomegaly, 15 cm, hepatomegaly 19 cm	Luspatercept 1 mg/kg SC q3 weekly x 6 months; then1.25 mg/kg SC q3 weekly	Initially asymptomatic. Later developed chest wall pain.	**MR spine pre-luspatercept**: multiple bilateral markedly T2 hyperintense paraspinal soft tissue masses. largest (right) measuring ~2.4 cm x 3.4 cm. The largest (left)-sided mass , T11, measures ~2.3 cm x 3.0 cm, previously ~1.4 cm x 2.6 cm. The left paraspinal mass ,T10 measures 1.9 cm x 3.3 cm, previously 1.4 cm x 2.6 cm **Post 16 months luspatercept therapy CT chest enhanced:** Bilateral paraspinal masses, interval enlargement since previous MRI 2021. Largest (right) measures 4.0 x 2.8 x 3.3 cm [previously 3.7 x 2.5 x 2.8 cm]. The largest (left) measures 4.3 x 2.7 x 2.9 cm [previously 3.4 x 2.0 x 2.7 cm on 2021 and 2.4 x 1.6 x 2.2 cm on previous MRI 2018].	**Initial therapy:** continue luspatercept, increase transfusion threshold. **Subsequently post symptoms**, discontinue luspatercept hydroxyurea initiated, target highest tolerated dose	Repeat spine MR pending after development of symptoms

Figure 1

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