Extramedullary Hematopoiesis in the Sinonasal Cavity: A Case Report and Review of the Literature

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Abstract
Background: Extramedullary hematopoiesis (EMH) occurs in patients with hematologic disorders, but rarely within the paranasal sinuses. We report a case of EMH in a 17-year-old male with sickle cell disease (SCD) who presented with occipital pain and sinusitis. A computed tomography (CT) scan demonstrated heterogeneous opacification of the right maxillary sinus concerning for allergic fungal sinusitis or a fungal ball with bony erosion. He was taken to the operating room for endoscopic biopsy and a limited endoscopic sinus surgery. Grossly, his maxillary sinus was filled with spiculated osseous tissue. Final pathology demonstrated active hematopoietic bone marrow filling the sinus.

Methods: We present a case report and literature review of sinonasal EMH.

Results: We identified 14 articles with 15 patients. EMH was typically associated with SCD or beta thalassemia. The average age of presentation was 30. There was a male sex predilection with a ratio of 11:15. The most common presenting symptom was a headache and nasal obstruction (33% for both). The most common finding on CT was a soft tissue expansile mass (73%). The most commonly affected location was the maxillary sinus (60%).

Conclusions: This case report serves as a reminder to consider EMH as an uncommon cause of sinus opacification, particularly in patients with SCD or beta thalassemia. The expansion of hematopoietic tissue may be identified as a sinus mass on CT. By recognizing the potential manifestations of chronic anemia, an accurate and timely diagnosis can be made.

Keywords
extramedullary hematopoiesis, sickle cell anemia, paranasal sinus, sinonasal mass, sinus tumor

Introduction
Approximately 1 in 600 African-Americans are homozygous for the sickle cell gene.1 This commonly inherited hematologic disorder causes sickling of red blood cells (RBCs), prompting rapid hemolysis. A common clinical manifestation of sickle cell disease (SCD) is chronic anemia. The body responds by increasing hematopoiesis. RBC production classically occurs in the bone marrow of the long bones, pelvis, spine, and sternum.1 With chronically elevated erythropoietin levels, organs such as the spleen and liver help augment the body’s RBC supply.2 These organs are areas of fetal erythropoiesis that do not typically contribute to physiologic RBC production in adults. Other, less commonly involved organs that have been documented as sites of extramedullary hematoposesis (EMH) include lymph nodes, paravertebral regions, intra-spinal canal, pre-sacral region, nasopharynx, and paranasal sinuses.3

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| Year | Author          | Age | M/F | Laterality | Comorbidity          | Presenting Symptoms                                                  | CT Findings                                                                 | Diagnosis/Intervention          |
|------|----------------|-----|-----|------------|----------------------|-----------------------------------------------------------------------|-----------------------------------------------------------------------------|---------------------------------|
| 1984 | Andreou et al. | 10 y/o | M | Bilateral | Beta thalassemia     | Seizures, progressive aphasia                                         | Bilateral expansile masses (ethmoid and maxillary involvement)              | Unknown                        |
| 1995 | Fernandez et al. | 28 m/o | M | Bilateral | SCD (HbSS)          | Sinusitis, rhinorrhea, fever, and respiratory distress                | Maxillary sinus opacification and enlargement                                | Left maxillary sinus biopsy     |
| 2000 | Joseph et al.  | 18 y/o | M | Unilateral | Beta thalassemia, SCD | Left focal motor seizure, mild anemia                                | Dense lesion in sphenoid sinus                                              | Transnasal biopsy               |
| 2001 | Vargas et al. | 71 y/o | F | Unilateral | Myelofibrosis       | Nasal mass, recurrent epistaxis                                      | Expansile mass in maxillary sinus                                           | Endoscopic biopsy               |
| 2002 | Kearney and Nasser | 24 y/o | M | Bilateral | Beta thalassemia major | Progressive weakness in lower extremities, urinary retention, and constipation | Masses in the maxillary and sphenoidal sinuses                              | Biopsy                         |
| 2003 | Rizzo et al.  | 68 y/o | F | Bilateral | Paget’s disease     | Left-sided diplopia and exophthalmos                                 | Expansile sphenoid mass with destruction of bony septa                     | Biopsy                         |
| 2004 | Brennan et al. | 72 y/o | M | Unilateral | Myeloproliferative disorder | Nasal obstruction                                                     | Unremarkable                                                                | Polyp removal and biopsy        |
| 2005 | Collins et al. | 13 y/o | M | Bilateral | SCD (HbSS)          | Nasal obstruction, bifrontal headache, rhinorrhea, facial pain       | Opacification of maxillary and anterior ethmoids sinus with intrasinus calcifications | Endoscopic sinus surgery and biopsy |
| 2007 | Ittipunkul et al. | 13 y/o | F | Bilateral | Beta thalassemia, HbE | Progressive vision loss, marked pallor                               | Expansile mass from ethmoid into sphenoid sinus                             | Monthly blood transfusion and low-dose radiotherapy (clinical diagnosis) |
| 2008 | Stamatakis et al. | 12 y/o | M | Unilateral | SCD                  | Nasal obstruction                                                     | Right maxillary sinus mass obstructing the right osteomeatal complex       | Right endoscopic sinus surgery and biopsy |
| 2010 | Bizzoni et al. | 30 y/o | M | Unilateral | Idiopathic thrombocytopenia | Frequent epistaxis, right nasal fossa obstruction, frontal headache | Expansile mass from maxillary sinus with bony remodeling                     | Transnasal endoscopic biopsy and complete resection                      |
| 2010 | Bizzoni et al. | 29 y/o | M | Unilateral | Intermediate beta thalassemia | Left nasal fossa obstruction, vertex headache, fever                  | Expansile lesion from posterior ethmoid into sphenoid sinus                 | Drainage of fluid with histologic analysis                                 |
| 2011 | Dorton and Mims | 41 y/o | F | Bilateral | Beta thalassemia     | Recurrent epistaxis                                                  | Diffuse marrow expansion with complete obliteration of maxillary sinus     | Manage epistaxis (clinical diagnosis)                                      |
| 2012 | Sklar et al.   | 14 y/o | M | Unilateral | SCD                  | Frontal headache                                                     | Expansile mass from sphenoid sinus                                         | Biopsy                         |
| 2014 | Reiersen et al. | 4 y/o | M | Bilateral | SCD (HbSS)          | Left-sided headache, pain, rapid progression of peri-orbital swelling, bilateral proptosis | Bilateral expansive maxillary heterogenous soft tissue opacification       | Biopsy and exchange transfusion                                         |

Abbreviations: CT, computed tomography; HbE, hemoglobin E; HbSS, homozygous sickle cell disease; SCD, sickle cell disease.
There are 2 types of EMH, extraosseous and paraosseous. The extraosseous form occurs in organs with multipotent stem cells, such as the spleen and liver, that can produce hematopoietic foci remote from bone marrow. This is seen in conditions that prevent effective production of RBCs within the marrow, such as myelofibrosis. Patients typically develop splenomegaly or hepatomegaly that may manifest as early satiety, bloating, pressure, or abdominal pain. In contrast to extraosseous EMH, paraosseous EMH occurs just outside of the bone due to the herniation of hyperactive marrow. This is more common in patients with SCD and thalassemias when erythroid marrow activity is high. Paraosseous EMH may remain clinically silent until there are enough cells to form a tumor-like mass associated with symptoms.

Although it is rare to see EMH within the sinonasal cavity, based on our literature review we believe this is the 16th reported case (Table 1). The presence of EMH within the sinonasal cavity is hypothesized to occur in the paraosseous form, with the herniation of marrow out of the expanding sinus wall into the sinus cavity. We present a case and discuss the challenges of diagnosis and treatment.

Case Presentation

A 17-year-old African-American male with SCD presented to his primary care physician with a 1-month history of severe occipital head pain, left facial numbness, and left eye droop. His SCD had previously caused several emergency department admissions for pain and sickle cell crisis. Magnetic resonance imaging (MRI) was ordered to rule out a possible skull infarct secondary to a sickle cell crisis. The MRI image did not show an infarction, but the patient’s left maxillary sinus was completely opacified and enlarged compared to the contralateral side. He was referred to otolaryngology for further evaluation.

The patient presented to otolaryngology clinic with sinusitis and occipital pain. The physical examination was normal, but nasal endoscopy demonstrated medialization of the uncinate and medial maxillary wall within the left nasal cavity. There were no polyps or purulence noted on either side. A noncontrast computed tomography (CT) was ordered and revealed opacification and expansion of the left maxillary sinus that occluded the ostiomeatal unit consistent with a fungal ball (Figure 1(A) and (B)). Due to the persistent symptoms and unknown etiology of the sinus lesion, the patient was scheduled for endoscopic sinus surgery. Intraoperatively, the maxillary sinus was noted to filled with spiculated osseous tissue (Figure 2). A routine maxillary antrostomy was performed and specimens were collected for pathology. No drilling or special techniques were required. Pathology demonstrated erythroid hyperplasia with blood cells of all 3 hematopoietic lineages intermixed with fragments of bone (Figure 3(A) and (B)).

The patient was observed postoperatively without complications and discharged home. He has not experienced any subsequent episodes of facial pressure or pain since the surgery. Nevertheless, he continues to have frequent exchange transfusions and struggles with pain management for his underlying SCD.

Methods

Data for the case report were collected from the electronic medical health record. A literature review was performed by searching the following keywords in PubMed: extramedullary hematopoiesis and paranasal sinus. Fifteen articles were identified (Figure 4). After reviewing the abstracts, 5 articles were excluded, because they did not describe clinical patients with extramedullary hematopoiesis of the paranasal sinuses. References from the remaining 10 articles were searched for additional pertinent cases and case series. We identified an additional 4 articles, for a total of 14 articles with 15 patients. A table was compiled to organize the data (Table 1).
EMH was typically associated with SCD or beta thalassemia, with an equal prevalence of each among the cases reviewed. There was a male sex predilection with 11 of 15 of the cases occurring in male patients. The average age of presentation was 30, with a minimum age of 28 months and a maximum of 72 years. The median age was 18 years. Interestingly, the 3 oldest patients had acquired conditions rather than inherited defects. Two of the patients had myeloproliferative disorders and the other had Paget’s disease.

Any sinus can theoretically be affected, but the most commonly affected location was the maxillary sinus. There were 9 cases with maxillary involvement, 6 with sphenoid involvement, and 4 with ethmoid involvement. Nasal obstruction and/or headache was a presenting symptom in 33% of patients. Recurrent epistaxis was the presenting symptom in 20% of patients. One reported case of sinonasal EMH was incidentally identified on CT scan after a motor vehicle collision.

Discussion
EMH can present as a sinus opacification in patient chronic anemia from diseases such as thalassemias, SCD, and myeloproliferative disorders. After reviewing the literature, common themes were identified in the detection and diagnosis of EMH (Table 1).
CT imaging, the hematopoietic tissue typically appears as a soft tissue mass that may demonstrate calcifications. Several cases involving the paranasal sinuses showed bone remodeling, bulging, and protrusion into other sinuses. These findings may resemble the appearance of allergic fungal sinusitis on imaging, and thus many of the pre-operative diagnoses included fungal etiologies. However, in the few cases that utilized MRIs, sinonasal EMH demonstrated signal intensity and enhancement similar to that of red bone marrow.1

No definitive therapeutic guidelines for paranasal sinus EMH exist. Twelve of 15 cases proceeded with a biopsy to confirm the diagnosis and to exclude neoplasm. Several authors have suggested that the hematopoietic tissue should not be removed, as it serves as a vital contributor to the patient’s RBC reserve.6 In addition to surgery, 2 of 15 patients were treated with exchange transfusions which serve to address the underlying anemia and decrease the demand on the extramedullary marrow.7 Normalization of hematocrit levels suppresses the hematopoietic foci to the extent that it no longer produces symptoms. Even in the more serious cases, with seizures, proptosis, and vision loss as presenting symptoms, patients were successfully managed with conservative management.

Conclusions
Extramedullary hematopoiesis within paranasal sinuses is a rare diagnosis in a patient with chronic anemia. Imaging is frequently concerning for allergic fungal sinusitis. A biopsy is required to diagnose EMH and rule out an underlying malignancy. We recommend that EMH be included in the differential diagnosis of a soft tissue, expansile sinus mass presenting in patients with known hematologic conditions.

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Ethical Approval
This study was approved by our institutional review board.

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References
1. Saito N, Nadgir RN, Flower EN, Sakai O. Clinical and radiologic manifestations of sickle cell disease in the head and neck. *RadioGraphics*. 2010;30(4):1021–1034.
2. Stamataki S, Behar P, Brodsky L. Extramedullary hematopoiesis in the maxillary sinus. *Int J Pediatr Otorhinolaryngol*. 2009;4(1):32–35.
3. Sohawon D, Lau KK, Lau T, Bowden DK. Extra-medullary haematopoiesis: a pictorial review of its typical and atypical locations. *J Med Imaging Radiat Oncol*. 2012;56:538–544.
4. Lund RE and Aldridge NH. Computed tomography of intracranial extramedullary hematopoiesis. *J Comput Assist Tomogr*. 1984; 8:788–790.
5. Kearney PR, Nasser A. Pathology quiz case 2. *Arch Otolaryngol Head Neck Surg*. 2002;128(1):76.
6. Collins WO, Younis RT, Garcia MT. Extramedullary hematopoiesis of the paranasal sinuses in sickle cell disease. *Otolaryngol Head Neck Surg* 2005;132(6):954–956.
7. Reiersen DA, Mandava M, Jeroudi M, Gungor A. Maxillofacial extramedullary hematopoiesis in a child with sickle cell presenting as bilateral periorbital cellulitis. *J Med Imaging Radiat Oncol*. 2012;56:538–544.
8. Andreou J, Gouliamos A, Kalovidouris A, Papailiou J, Papavasiliou C. Bone marrow hyperplasia of the maxillary sinuses in β-thalassemia. *J Comput Assist Tomogr*. 2014;78(7):1173–1175.
9. Andreou J, Gouliamos A, Kalovidouris A, Papailiou J, Papavasiliou C. Bone marrow hyperplasia of the maxillary sinuses in β-thalassemia. *J Comput Assist Tomogr*. 1984; 8(1):180.
10. Fernandez M, Slovis TL, Whitten-Shurney W. Maxillary sinus marrow hyperplasia in sickle cell anemia. *Pediatr Radiol*. 1995;25:S209–S211.
11. Joseph M, Rajshekharr V, Chandy M. *Neuroradiology*. 2000;42:153.
12. Vargas H, Jennings TA, Galati LT. Unusual paranasal sinus tumors in two patients with common nasal complaints. *Ear Nose Throat J*. 2001;80(10):724–729.
13. Rizzo L, Greco Crasto S, Tola E, Sardo P, Rubino A. Extramedullary hematopoiesis: unusual meningeal and paranasal sinuses presentation in Paget disease. Case report. *La Radiol Med*. 2003;105(4):376–381.
13. Brennan LV, Mayer T, Devitt J. Extramedullary hematopoiesis occurring as a nasal polyp in a man with a myeloproliferative disorder. *Ear Nose Throat J*. 2004; 83(4):258–259.

14. Ittipunkul N, Martin T, Siriwanasan R, Olanratanachai K, Rootman J. Extra-medullary hematopoiesis causing bilateral optic atrophy in beta thalassemia/Hb E disease. *J Med Assoc Thailand*. 2007;90(4):809–812.

15. Bizzoni A, Lombardi D, Maroldi R, Incardona P, Nicolai P. Extramedullary hematopoiesis: a rare occurrence in the sinonasal tract. *Auris Nasus Larynx*. 2010;37(2):233–237.

16. Dorton LH, Mims JW. Extramedullary hematopoiesis of the maxilla in beta-thalassemia. *Otolaryngol Head Neck Surg*. 2011;145:P259.

17. Sklar M, Rotaru C, Grynspan D, Bromwich M. Radiographic features in a rare case of sphenoid sinus extramedullary hematopoeisis in sickle cell disease. *Int J Pediatr Otorhinolaryngol*. 2013;77(2):294–297.