Isolated granulocytic sarcoma of the nasopharynx: a case report and review of the literature

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Abstract: Granulocytic sarcoma (GS) is a rare extramedullary manifestation of acute myeloid leukemia (AML). It may also represent blastic transformation of myelodysplastic syndromes or myeloproliferative neoplasms. Although usually seen in the context of advanced and poorly controlled disease, it may also present as the first manifestation of illness, without concurrent bone marrow or blood involvement. In the medical literature, chloroma and GS are terms that have been used interchangeably with myeloid sarcoma. GS usually manifests as soft tissue or bony masses in several extracranial sites, such as bone, periosteum, and lymph nodes; involvement of the head and neck region is uncommon. We report a case of a woman with insidious onset of progressive nasal congestion and diminished hearing who was diagnosed with an isolated GS of the nasopharynx. With involved field radiotherapy, she achieved a complete remission of 12-months duration before being diagnosed with overt AML. She has remained disease-free for greater than 18 months following induction and consolidation chemotherapy. Through a MEDLINE®/PubMed® search we identified an additional 13 cases of nasopharyngeal GS. The median age was 37 years (range 1 to 81 years). The cases were equally distributed among the sexes. The most common presenting symptoms were conductive hearing loss and sinonasal congestion. Isolated GS was identified in six cases, and the median time from diagnosis of GS to AML was 12 months (range 3 to 48 months). The treatment varied, but responses were seen in all the patients who received chemotherapy with or without radiotherapy.

Keywords: acute myeloid leukemia, myeloid sarcoma, chloroma, treatment

Introduction
Acute myeloid leukemia (AML) may occur in a variety of extramedullary (EM) tissues, with or without bone marrow disease. Two well-known EM manifestations of AML are granulocytic sarcoma (GS) and leukemia cutis. GS, also known as myeloid sarcoma or chloroma, is a rare EM tumor of immature myeloid cells.1 The high expression of myeloperoxidase (MPO) makes these tumors appear green hence, the name “chloroma” (from the Greek “chloros,” meaning green).2 GS can develop de novo or concurrently with AML, myeloproliferative neoplasms (MPNs) or myelodysplastic syndromes (MDSs).1,3–6 Isolated GS defined by the absence of a history of AML, MDS, or MPN, and unremarkable blood and bone marrow analyses has been described, albeit sparsely.7–9 GS, most commonly see in the context of widespread and uncontrolled disease, may also be the first manifestation of AML, antedating it by months or years, or represent the initial manifestation of relapse in a patient previously treated for AML.10,11 The risk factors for GS include specific chromosomal abnormalities, such as translocations between chromosomes 8 and 21 (t[8;21]) and...
inversion of chromosome 16 (inv[16]), the expression of cell-surface markers (cluster of differentiation [CD]56, CD2, CD4, and CD7), and the French–American–British (FAB) classification M2, M4, and M5 leukemia subtypes. Additional risk factors include poor nutritional status, cellular immune dysfunction, high presenting leukocyte count, and decreased blast Auer rods.\(^{11,12}\) GS is slightly more common in men than in women (male to female ratio, 1.42:1).\(^{13}\) While various body sites have been associated with GS, the most common locations include soft tissue, bone, perosteum and the lymph nodes.\(^{9,12}\) Here, we describe the case of a female with GS manifesting as a nasopharyngeal mass that was treated with radiation therapy, after which AML manifested 12 months later. We also review the literature of previously reported cases of nasopharyngeal GS and focus on the clinical presentation, diagnosis, and the treatment of this disorder.

**Case report**

A 63-year-old Caucasian female sought evaluation in the Otolaryngology clinic (Virginia Mason Medical Center, Seattle, WA, USA) due to decreased hearing in her left ear and progressive nasal congestion. Prior to that visit, she had been treated empirically for several months with various antibiotics and decongestants and briefly with intranasal steroids. Her chronic medical problems were notable for nonallergic rhinitis, hypertension, hyperlipidemia, and morbid obesity. Her general and cranial nerve exam were unremarkable, but she was identified as having conductive hearing loss due to a left middle ear effusion. On sinonasal endoscopy, an excoriated mass was also identified, involving the posterior nasopharynx and nasal turbinates. A biopsy of the mass revealed intermediate-sized blastic cells that stained positive for MPO, CD68 (dim), CD99, and CD117 (dim), consistent with involvement by GS (Figure 1). The results of the laboratory studies included a normal complete blood count (CBC) as well as unremarkable serum chemistry and liver enzyme levels. A flow cytometry study of the circulating white cells was also unremarkable, as having conductive hearing loss due to a left middle ear effusion. The tumor cells were negative for human leukocyte antigen (HLA)-DR, CD34, CD13, CD14, CD15, CD64, CD2, CD3, CD4, CD5, CD7, CD56, CD71, and CD38. The results of the laboratory studies included a normal complete blood count (CBC) as well as unremarkable serum chemistry and liver enzyme levels. A flow cytometry study of the circulating white cells was also unremarkable, as having conductive hearing loss due to a left middle ear effusion. The tumor cells were negative for human leukocyte antigen (HLA)-DR, CD34, CD13, CD14, CD15, CD64, CD2, CD3, CD4, CD5, CD7, CD56, CD71, and CD38. The phenotype was similar to the phenotype of the myeloid blasts identified in her prior nasopharyngeal biopsy. Band karyotyping of the peripheral blood blasts showed normal (46, XX) cytogenetics. Induction chemotherapy was prescribed, consisting of cytarabine (100 mg/m\(^2\)/day, days 1–7) and idarubicin (13 mg/m\(^2\)/day, days 1–3).\(^{14}\) Her clinical course was notable for mild mucositis, fluctuating blood sugars, and culture-negative neutropenic fever. A bone marrow aspirate and biopsy obtained on day 14 was markedly hypocellular; a repeat bone marrow biopsy on day 28 was normocellular, with maturing trilineage

Figure 1 Biopsy of the nasopharyngeal mass, showing sheets of intermediate-sized blasts with round nuclei, dispersed chromatin, distinct nucleoli, and small amounts of cytoplasm. The tumor cells stained positive for myeloperoxidase and weakly for CD117.

Abbreviation: CD, cluster of differentiation; MPO, myeloperoxidase; H&E, hematoxylin and eosin.
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hematopoiesis and no residual leukemia. She went on to receive an additional three cycles of consolidation therapy, with continuous infusion cytarabine and bolus idarubicin (5+2 regimen). She remains in remission, with a normal CBC at the 18-month follow-up visit.

Discussion and literature review

GS is an infrequently diagnosed condition. It is reported in about 2.5%–9.1% of patients with AML. While it can be solitary or multifocal, most cases manifest as isolated single lesions. The most common sites of EM involvement of AML include the skin (leukemia cutis), lymph node, and bone, but other sites, including the female reproductive tract, breast, gut, and testis have been reported. In the head and neck region, GS will usually involve the orbits, and only rarely will it affect the nasopharynx. Utilizing a MEDLINE®/PubMed® search, with the key words “granulocytic/myeloid sarcoma,” “chloroma,” “nasopharynx,” and “acute myeloid leukemia” and restricting our search to the English language reports between the years 2000–2013, we identified 13 additional patients between the ages of 1 to 81 years (median age of 37 years) with GS involving the nasopharynx (Table 1). The male to female ratio within the group was 1:1. Sinonasal congestion or hearing loss was the reason why most patients sought medical attention. The longest reported disease-free interval from diagnosis was 36 months. Among the seven cases where the disease-free interval was reported, the median was 18 months (range, 4 to 36 months).

In the absence of circulating myeloblasts, GS is seldom considered in the initial differential diagnosis of a soft tissue mass. Its similarity, both radiographically and histopathologically, to other small round cell tumors, such as lymphoblastic leukemia, melanoma, Ewing sarcoma, blastic plasmacytoid dendritic cell neoplasm, as well as certain forms of non-Hodgkin lymphoma and benign EM hematopoiesis means that there may be a delay in diagnosis while the clinician waits for supportive diagnostic tests from the pathologist. GS typically consists of a diffuse and infiltrative population of myeloblasts and granulocytic cell types. Infrequently, tumors can occur in the setting of trilineage hematopoiesis or erythroid or megakaryocytic precursors, particularly in cases of transformation from MPN. Immunohistochemistry is useful for establishing the diagnosis of GS and can be easier to perform than flow cytometry, which requires fresh tissue. Immunohistochemical markers, such as CD68, MPO, lysozyme, and CD43, can assist in differentiating between myeloid and nonmyeloid cells.

Myelocytic differentiation may also be confirmed by Leder stain (chloroacetate esterase), CD117, CD34, and terminal deoxynucleotidyl transferase (TdT) are useful as markers of immaturity. When GS is found in an EM location and in the absence of circulating blasts, a bone marrow biopsy is necessary to rule out concurrent marrow involvement. Cytogenetic abnormalities are seen in roughly 50% of cases and include monosomy 7, trisomy 8, inv(16), t(9;11), deletion (del)(16q), t(8;16), and t(1;11). Nucleophosmin (NPM1) mutations have been reported in 15% and FMS-related tyrosine kinase 3 (FLT3) gene mutations in 20%–30% of GS cases; however, the clinical significance of NPM1 and FLT3 mutation in this clinical context remains uncertain.

A CT scan is best for evaluating soft tissue GS, and magnetic resonance imaging (MRI) with gadolinium is preferred when GS involves the central nervous system. A PET scan may be helpful for detecting additional sites of EM AML and also for planning local (eg, radiotherapy) treatment and/or systemic chemotherapy. It can also be used for monitoring the response to treatment. For patients who achieve a complete remission with treatment, the...
Table 1 Case reports of granulocytic sarcoma involving the nasopharynx

| Reference         | Age (years), sex | Clinical features                                      | Associated diagnosis         | Cytogenetics | Outcome                                    |
|-------------------|-----------------|-------------------------------------------------------|-----------------------------|--------------|---------------------------------------------|
| Bassichis et al21 | 1, male         | Masseter muscle                                       | Synchronous AML             | NR           | Died during chemotherapy                    |
| Au et al22        | 37, male        | Conductive hearing loss, infiltrative nasopharyngeal mass | Solitary site of GS         | Normal       | IFRT and chemotherapy. CR at 3 years       |
| Nayak et al21     | 24, female      | Bilateral parotid and nasopharyngeal mass             | Solitary site of GS         | NR           | Patient died on 17th day of chemotherapy, due to systemic infection |
| Geisse et al24    | 60, male        | Waldeyer’s ring lymphadenopathy                        | Synchronous MDS             | NR           | Diagnosis made on autopsy                   |
| Prades et al32    | 20, female      | Sinonasal obstruction; right maxillary and sphenoid sinus mass | GS of the nasal cavity and paranasal sinus | t(19:1)     | AHSCT following chemotherapy; CR at 18 months |
| Ozcelik et al24   | 37, male        | Vocal cord paralysis, involvement of 9th, 10th, and 12th cranial nerves | AML (M0) 6 months earlier – treated with chemotherapy to CR | NR           | Treated with chemotherapy with partial regression of the nasopharyngeal masses; patient died on 17th day of chemotherapy due to pulmonary infection |
| Sugimoto et al27  | 31, female      | Nasopharynx, external acoustic meatus                  | AML (M2) 3 months earlier – treated with chemotherapy to CR | t(8;21)(q22;q22) | Achieved CR2 with IFRT, induction chemotherapy, followed by AHSCT |
| Imamura et al4    | 7, female       | Waldeyer’s ring and cervical lymphadenopathy           | Synchronous juvenile myelomonocytic leukemia | t(9;12) (p22;q24.1) | AHSCT following chemotherapy; CR at 3 years |
| Ferri et al18     | 72, female      | Right facial swelling and fever; maxilla-ethmoidal mass | AML (M0) 1 year earlier – treated with hydroxyurea | NR           | Best supportive care only; died after 10 days of hospitalization |
| Teramoto et al23  | 81, female      | Nasopharyngeal mass                                    | Developed AML (M2) 1 year later | Complex genomic defects on cDNA microarray | Radiation therapy only for GS; chemotherapy for AML; died 6 months after diagnosis of AML |
| Selvarajan et al19| 25, male        | Dysphagia, hoarseness, facial nerve palsy              | AML (M2) 4 years earlier – treated with chemotherapy to CR, followed by AHSCT | t(8:21)      | Treated with chemotherapy but had systemic relapse 1 year later |
| Cho et al16       | 18, male        | Conductive hearing loss, infiltrative nasopharyngeal mass | Synchronous AML             | RUNX1-RUNX1T1 | Recurrence after 7 months of chemotherapy; achieved CR2 with induction chemotherapy, followed by AHSCT |
| Mei et al20       | 56, female      | Left maxillary sinus                                  | Solitary site of GS         | NR           | Surgical resection followed by chemotherapy; CR at 4 months |
| (Current) case    | 63, female      | Conductive hearing loss, infiltrative nasopharyngeal mass | Developed AML 1 year later | Normal       | Radiation therapy only for GS; chemotherapy for AML; CR at 18 months |

Abbreviations: AHSCT, allogeneic hematopoietic stem cell transplant; AML, acute myeloid leukemia; cDNA, complementary deoxyribonucleic acid; CR, complete remission; CR2, second CR; GS, granulocytic sarcoma; IFRT, involved-field radiotherapy; MDS, myelodysplastic syndrome; NR, not reported; t, translocation.

role of routine monitoring with radiographs has not been established.32 The treatment of GS depends upon patient and disease characteristics. The patient’s age, associated medical comorbidities, clinical symptoms, tumor karyotype, stage, and the extent of disease are important factors to be considered before planning treatment. There are no randomized studies to help guide the treatment choices, and the GS location does not appear to impact survival. Chemotherapy (both systemic and intrathecal), radiation therapy, surgical extirpation, or any
combination of these interventions have all been employed (Table 2). Remission-induction chemotherapy similar to that used for AML is favored for either isolated GS or GS presenting with concomitant AML.43,44 Significantly longer disease-free intervals without leukemia have been achieved in patients with isolated GS who received systemic chemotherapy rather than surgery or radiation therapy, belying the fact that this is inevitably the first manifestation of a systematic disease.45,46 Surgery is generally reserved for cases with acute symptoms (eg, pain, acute nerve compression), and at times, to obtain an adequate tissue sample following a nondiagnostic fine-needle aspiration.

The role of allogeneic hematopoietic stem cell transplantation (AHSCT) in patients with GS has not been studied prospectively, but improved outcomes with AHSCT have been reported in repeated retrospective analyses.1,47 In a retrospective study of 51 patients with GS, either isolated or associated with AML, the 5-year overall survival was 48%, with no significant differences in outcomes between the two presentations.48 For those patients with GS and graft-versus-host disease, there was a trend toward improved overall survival.

Patients with a history of GS are at risk for relapse, and careful assessments at follow-up appointments are needed as early isolated GS can be asymptomatic.49 A biopsy of any new or suspicious soft tissue or skin abnormality should be performed, and if no circulating blasts are present, a bone marrow biopsy is necessary.52 For patients who relapse after chemotherapy, reinduction chemotherapy may be an option if there has been a long disease-free interval after the initial treatment. For those individuals who are deemed hardy enough and who have an identified HLA match, AHSCT is the preferred consolidative approach. When bone marrow and EM relapse occurs synchronously after AHSCT, survival is very poor and no standard treatment has proven effective, although donor lymphocyte infusions, tapering of immunosuppression, or investigational agents may be considered.50,51

Disclosure
The authors report no conflicts of interest in this work.

Table 2 Treatment approaches for granulocytic sarcoma

| Disease status                           | Suggested treatment approach                                      |
|-----------------------------------------|------------------------------------------------------------------|
| Isolated GS                             | Chemotherapy followed by surgery/radiation treatment             |
| GS with bone marrow involvement         | Chemotherapy with consideration for AHSCT                        |
| Relapsed isolated GS after chemotherapy | Chemotherapy followed by AHSCT                                    |
| Relapsed GS and bone marrow disease     | Chemotherapy followed by AHSCT                                    |
| after chemotherapy                      | Donor lymphocyte infusion, tapering of immunosuppression if tolerated, or investigational agents versus palliative IFRT |
| Relapse of isolated GS after AHSCT      | Investigational agents versus best supportive care               |
| Relapse of concurrent GS and bone       |                                                                  |
| marrow disease after AHSCT              |                                                                  |

Abbreviations: AHSCT, allogeneic hematopoietic stem cell transplant; GS, granulocytic sarcoma; IFRT, involved-field radiotherapy.

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