

Immunohistochemical patterns in the differential diagnosis of rhinopharyngeal granulocytic sarcoma

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Abstract. Granulocytic sarcoma (GS) is a rare extramedullary manifestation of acute myeloid leukemia (AML). GS may develop simultaneously to AML or as a relapse of leukemia, particularly following allogeneic hematopoietic stem cell transplant. Subperiosteal bone, lymph nodes and skin are commonly involved, whereas rhinopharyngeal involvement is less common, with only 14 cases reported in the literature. Due to its rarity, rhinopharyngeal GS may lead to diagnostic pitfalls, particularly when it is poorly differentiated or is without concomitant marrow involvement. Thus, immunohistochemical findings play a key role in diagnosis. The current report describes a case of a 53-year-old female suffering from rhinopharyngeal GS and with a history of AML treated with chemotherapy and radiotherapy, focusing on the importance of the immunohistochemical pattern to assess the right diagnosis. Recent studies have demonstrated that the immunophenotype is of utmost importance for the diagnosis of GS. The high expression of myeloperoxidase (MPO) is common in GS; however, ~30% of GSs do not contain MPO. Therefore, the presence of other markers is required to confirm the diagnosis of GS.

Introduction

Granulocytic sarcoma (GS) is a rare, extramedullary malignant neoplasm consisting of myeloid cells with different levels of maturation and occurring in anatomic sites other than the bone marrow or peripheral blood (1). It represents a distinct entity of AML (2).

The high expression of myeloperoxidase (MPO) makes these tumors green, hence their alternative name, 'chloroma' (from the Greek word 'chloros', meaning green). However,

'sarcoma' is the most commonly used term, as ~30% of these tumors do not contain MPO, despite the fact that MPO together with cluster of differentiation (CD)117 represents the marker for myeloid differentiation (1).

GS may develop *de novo* (solitary, primary or non-leukemic GS; 8-20%) (3), simultaneously to AML (2.5-9.1%) (4), or as a relapse of leukemia, particularly following allogeneic hematopoietic stem cell transplant (AHSCT) (4,5). The reason for this association is still unknown, but may be attributed to a pattern of graft-versus-leukemia surveillance or to the biology of high-risk AML treated with transplantation (5).

GS may affect patients of all ages (median age, 56 years; range, 1 month to 89 years), with a male:female ratio 1.2:1 (6). Commonly involved sites include subperiosteal bone, lymph nodes and skin. The prevalence of head and neck region involvement is 12-43% of cases (5), and orbit, skull and epidural spaces are the most frequently involved sites (7). Rare lesions have been described in the maxilla, soft palate, paranasal sinus, salivary gland, scalp and temporal bone, whereas only a few cases have been described with rhinopharyngeal involvement (4).

GS risk factors include specific chromosomal abnormalities [t(8;21) and inv(16)], expression of cell-surface markers (CD56, CD2, CD4 and CD7), and M2, M4 and M5 leukemia subtypes of the French-American-British classification (4). Additional risk factors include poor nutritional status, cellular immune dysfunction, high presenting leukocyte count and decreased blast Auer rods (4).

Sinonasal congestion and/or hearing loss are the most common clinical manifestations of rhinopharyngeal GS (4).

The diagnosis of the rhinopharyngeal GS, particularly when it is poorly differentiated or without concomitant marrow involvement, is challenging (8), and it is not uncommon for GS to be misdiagnosed as lymphoma (8,9). To improve the accuracy of diagnosis, immunohistochemical patterns play a key role. For instance, myeloid cells are reactive to antibodies against lysozyme, MPO and chloroacetate esterase. Furthermore, GS myeloblasts typically express myeloid-associated antigens, such as CD43, but are not reactive to lymphoid antigens. In addition, flow cytometry and cytogenetic analysis may aid in determining a definitive diagnosis (8).

GS is sensitive to focal irradiation and to systemic chemotherapy, similarly to AML (7,10,11). Systemic treatment should

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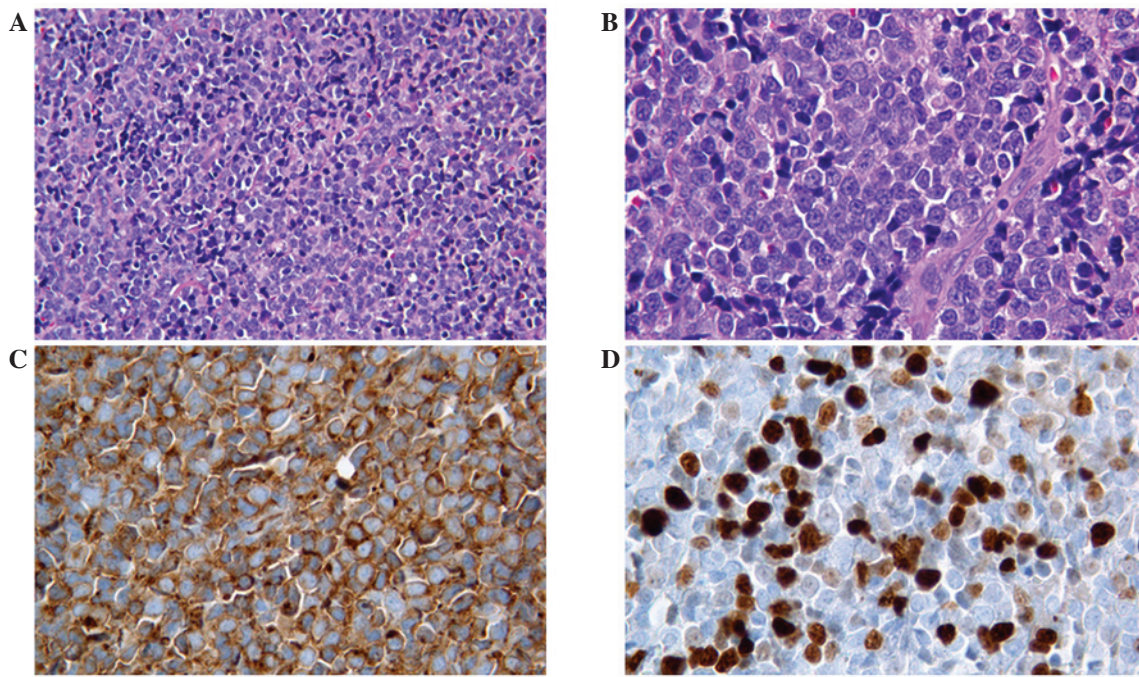


Figure 1. Histopathological analysis of biopsy specimen. (A and B) The neoplastic cell population was composed of small and medium sized elements, characterized by an inconspicuous eosinophilic cytoplasm and a nucleus with an irregular nuclear membrane; occasionally a small nucleolus was observed [hematoxylin and eosin staining; magnification, (A) x20 and (B) x40]. (C) Neoplastic cells were strongly immunoreactive for cluster of differentiation 43. (D) A high proliferative index was observed (Ki-67, 40%).

always be considered due to the high rate of recurrence and progression to AML (11). Surgery may be a therapeutic option only for tumors, which cause organ dysfunction (11). The role of radiotherapy and AHSCT as a consolidation regimen remains to be clearly established (10,11).

GS has an unfavorable prognosis. Its course is rapid with a high mortality rate, particularly when associated with AML, whereas patients without evidence of leukemia have a better prognosis (9); cases initially diagnosed as solitary GS without evidence of leukemia and treated with systemic chemotherapy have a more favorable prognosis (9).

The current study reports the case of a 53-year-old woman who presented with a rhinopharyngeal mass. The mass was diagnosed as an isolated extramedullary GS as a relapse of AML, which had been treated 7 years earlier with chemotherapy and AHSCT and was followed by complete remission. In addition, a review of the literature is reported, along with the examination of immunohistochemical features as a tool for the differential diagnosis of GS compared to other rare tumors of the rhinopharynx.

Case report

A 53-year-old female non-smoker presented to the Ear, Nose and Throat Unit of 'Federico II' University of Naples (Naples, Italy) complaining of left otalgia, hearing loss and nasal obstruction for ~5 months. The patient had a history of AML, which was in complete remission following high-dose chemotherapy and AHSCT, administered 7 years earlier.

A nasal endoscopy revealed a left rhinopharyngeal peritubular mass obstructing the left Eustachian tube. The audiological evaluation revealed left conductive hearing loss due to an ipsilateral middle ear effusion. No lateral cervical

palpable lymph nodes were found. Magnetic resonance imaging and positron emission tomography-computed tomography (CT) examinations revealed a mass of the rhinopharynx (6x3.5 cm; standardized uptake value, 5.7) without bone erosion.

Laboratory studies, including a normal complete blood count, unremarkable serum chemistry and normal liver enzyme levels, did not reveal any alteration. No evidence of increased blast cell count was observed in the bone marrow aspiration sample.

The specimen was formalin fixed and paraffin embedded. Immunohistochemistry was performed using the avidin biotin complex as a visualization system and 3,3'-diaminobenzidine as chromogen for the reaction, with pre-diluted antibodies (dilution, 1:100) against B-cell lymphoma-2 (Bcl-2; 790-4604, clone SP66; rabbit; Ventana Medical Systems, Inc., Tucson, AZ, USA), CD3 (790-4341; clone 2GV6; rabbit; Ventana Medical Systems, Inc.), CD5 (790-4451; clone SP19; rabbit; Ventana Medical Systems, Inc.), CD10 (790-4506; clone SP67; rabbit; Ventana Medical Systems, Inc.), CD20 (760-2531; clone L26; mouse; Ventana Medical Systems, Inc.), CD34 (790-2927; clone QBEnd/10; mouse; Ventana Medical Systems, Inc.), CD43 (760-2511; clone L60; mouse; Ventana Medical Systems, Inc.), CD56 (790-4465; clone 123C3; mouse; Ventana Medical Systems, Inc.), CD99 (790-4452; clone O13; mouse; Ventana Medical Systems, Inc.), CD117 (790-2951; clone 9.7; rabbit; Ventana Medical Systems, Inc.), Ki67 (M724029; clone MIB1; mouse; Dako, Glostrup, Denmark) and MPO (760-2659; rabbit polyclonal; Ventana Medical Systems, Inc.). The patient underwent biopsy of the rhinopharyngeal lesion, which revealed neoplastic proliferation of medium- and small-sized cells. These cells exhibited inconspicuous cytoplasm, nuclei with irregular membranes, occasionally a small nucleolus, diffuse karyorrhexis and high mitotic activity (Fig. 1).

Table I. Case reports of GS involving the nasopharynx.

| Author | Age, years /gender | Site/symptoms | Associated diagnosis | Cytogenetic findings | Treatment/outcome | Ref. |
|-------------------------|--------------------|--|---|--|--|------|
| Vishnu <i>et al</i> | 63/F | Conductive hearing loss; nasopharyngeal mass | Developed AML 1 year later | Normal | Radiation therapy only for GS; chemotherapy for AML; CR at 18 months | (4) |
| Raphael <i>et al</i> | 73/M | Left maxillary sinus, posterior ethmoidal cells | Synchronous MDS | t(3;21) | Chemotherapy; AML after 3 months; mortality during chemotherapy. | (10) |
| Bassichis <i>et al</i> | 1/M | Masseter muscle | Synchronous AML | NR | Mortality during chemotherapy | (16) |
| Au <i>et al</i> | 37/M | Conductive hearing loss; nasopharyngeal mass | Solitary GS | Normal | IFRT+chemotherapy; CR at 3 years | (17) |
| Nayak <i>et al</i> | 24/F | Bilateral parotid and nasopharyngeal mass | Solitary GS | NR | Mortality during chemotherapy | (18) |
| Geisse <i>et al</i> | 60/M | Waldeyer's ring lymphadenopathy | Synchronous MDS | NR | Diagnosis made on autopsy | (19) |
| Prades <i>et al</i> | 20/F | Sinonasal obstruction; right maxillary and sphenoid sinus mass | GS of the nasal cavity and paranasal sinus | t(19;1) | Chemotherapy+AHST; CR at 18 months | (20) |
| Ozcelik <i>et al</i> | 37/M | Vocal cord paralysis; involvement of 9th, 10th and 12th cranial nerves | AML 6 months earlier, treated with chemotherapy to CR | NR | Mortality during chemotherapy | (21) |
| Sugimoto <i>et al</i> | 31/F | Nasopharyngeal mass | AML 3 months earlier, treated with chemotherapy to CR | t(8;21) | CR2 achieved with IFRT, reinduction chemotherapy+AHST | (22) |
| Imamura <i>et al</i> | 7/F | Waldeyer's ring lymphadenopathy | Synchronous JMML | t(9;12) | Chemotherapy+AHST; CR at 3 years | (23) |
| Ferri <i>et al</i> | 72/F | Right facial swelling and fever; maxillo-ethmoidal mass | AML 1 year earlier, treated with hydroxyurea | NR | Best supportive care only; mortality after 10 days of hospitalization | (24) |
| Teramoto <i>et al</i> | 81/F | Nasopharyngeal mass | Developed AML 1 year later | Complex genomic defects on cDNA microarray | Radiation therapy only for GS; chemotherapy for AML; mortality 6 months after diagnosis of AML | (25) |
| Selvarajan <i>et al</i> | 25/M | Dysphagia, hoarseness, facial nerve palsy | AML 4 years earlier, treated with chemotherapy to CR followed by AHST | t(8;21) | Chemotherapy; systemic relapse 1 year later | (26) |
| Cho <i>et al</i> | 18/M | Conductive hearing loss; nasopharyngeal mass | Synchronous AML | t(8;21) | Recurrence after 7 months of chemotherapy; CR2 achieved with reinduction chemotherapy+AHST | (27) |
| Mei <i>et al</i> | 56/F | Left maxillary sinus | Solitary site of GS | NR | Surgical resection and chemotherapy; CR at 4 months | (28) |
| Current case | 53/F | Conductive hearing loss; nasopharyngeal mass | AML 7 years earlier, treated with chemotherapy to CR followed by AHST | Normal | Chemoradiation therapy; no sign of recurrence at 1 year | |

GS, granulocytic sarcoma; M, male; F, female; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; JMML, juvenile myelomonocytic leukemia; CR, complete remission; AHST, allogeneic hematopoietic stem cell transplant; NR, not reported; t, translocation; cDNA, complementary DNA; IFRT, involved-field radiotherapy; CR2, second complete remission.

The immunohistochemical evaluation revealed strong reactivity for CD43, CD34 and CD99, whereas CD20, CD3, CD5, CD10, Bcl-2, MPO, CD117 and CD56 were all negative. The Ki-67 proliferative index was ~40%. Fluorescence *in situ* hybridization (FISH) analysis was performed on 4- μ m-thick formalin-fixed, paraffin-embedded (FFPE) tissue sections, using the Vysis LSI Dual Color probe (Abbott Molecular, Inc., Des Plaines, IL, USA) specific for runt-related transcription factor 1 (RUNX1) labeled with Spectrum Green and for RUNX1T1 labeled with Spectrum Orange. The slides were hybridized overnight according to the manufacturer's protocol. Image analysis was then conducted. The FISH analysis of FFPE tumor slides did not identify either the t(8;21) translocation or *MLL* gene dissociation.

The patient's medical history and immunophenotype suggested the presence of a poorly differentiated extramedullary GS of the rhinopharynx as a relapse of AML, without bone marrow disease.

The patient was treated with conventional induction AML therapy: Combined idarubicin (12 mg/m²/day, days 1-2) and cytarabine (200 mg/m²/day, days 1-7), followed by one course of consolidation therapy with idarubicin (12 mg/m², day 1) and cytarabine (1 g/m²/12 h, days 1-5), as well as radiation treatment (1,500 cGy in 5 fractions).

A CT scan performed at 1 month after chemoradiotherapy revealed complete resolution of the rhinopharyngeal mass. At the 3-year follow-up, the patient was asymptomatic and without signs of recurrence. At present, the patient is under a regular surveillance protocol; she is closely monitored through a multidisciplinary 'short time' follow-up protocol, consisting of nasal endoscopy and blood studies every 3 months.

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

Discussion

GS, also known as 'chloroma' or 'extramedullary myeloblastoma', is a rare solid tumor consisting of primitive precursors of the granulocytic series of white blood cells, which include myeloblasts, promyelocytes, and myelocytes (1). Rhinopharyngeal localization of GS is extremely rare; only a few cases have been previously reported in the literature (4), and the present study reports the 15th case (Table I).

GS has a high rate of misdiagnosis (46%) (12,13), and its differential diagnosis may include non-Hodgkin's lymphoma (lymphoblastic, Burkitt and diffuse large B-cell lymphomas), lymphoblastic leukemia, melanoma, Ewing's sarcoma, primitive neuroectodermal tumor, rhabdomyosarcoma, neuroblastoma, medulloblastoma, undifferentiated carcinoma, blastic plasmacytoid dendritic cell neoplasm, extramedullary hematopoiesis (13) and small undifferentiated round cell tumors (6,14).

Previous studies have demonstrated that immunophenotype is of utmost importance in determining the diagnosis of GS (3-5). In particular, the literature has focused on the CD13 and CD68 markers for granular monocytic and macrophagic cells, MPO and CD117 markers for myeloid differentiation, lysozyme marker for monocytic lineage, CD43 marker for myeloid cells as well as T cells and B precursors, and CD34 and terminal deoxynucleotidyl transferase (TdT) markers for immature cells (10). Immunohistochemical detection of

intracellular MPO, a major constituent of primary granules of neutrophilic myeloid cells, confirms a diagnosis of GS. However, while MPO is expressed in the majority of GSs, some minimally differentiated and monocytic GSs do not express it (8).

CD68-KP1 is the most commonly expressed marker, followed by MPO, CD117, CD99, CD68/PG M1, lysozyme, CD34, TdT, CD56, CD61/linker of activated T lymphocyte/factor VIII-related antigen, CD30, glycophorin A and CD4 (3). Rarely, aberrant antigenic expression is observed (such as cytokeratins, B- or T-cell markers) (3).

In the current case, immunohistochemical evaluation revealed strong reactivity for CD43, CD34 and CD99, whereas MPO was negative. In particular, the presence of CD99 made it difficult to differentiate GS from other CD99-positive round cell tumors (14), whereas the positivity for CD34 (15) and the negativity for MPO indicated the presence of a mass of immature cells. In the present case, the clinical history of previous AML was the key to the specific diagnosis of GS.

From a therapeutic perspective, data from the literature suggest that GSs are extremely sensitive to focal irradiation or chemotherapy; however, their role is not well defined (13,16-28). The optimal treatment for the GS-AML association remains uncertain. However, high-dose chemotherapy and stem cell transplantation may be the treatment of choice (6).

The risk of metachronous AML in non-leukemic patients with GS is very high, with a median delay of 5 months; the majority of patients may develop AML within 1 year. Therefore, early intensive (induction/intensification) chemotherapy similar to that used to treat AML must be administered, even in GS patients without AML upon initial diagnosis (6).

Byrd *et al* stated that 97% of all primary GS patients who did not receive systemic chemotherapy developed AML (12). Furthermore, 66% of patients who received chemotherapy for the primary GS did not develop AML, suggesting that early systemic therapy is helpful in preventing AML, which increases the overall survival time (6).

Literature data demonstrated that clinical behavior and response to therapy are not influenced by any of the following factors: Age, gender, anatomic site, *de novo* presentation, histotype, phenotype or cytogenetic findings (6).

In the current case, given the previous history of AML and according to data in the literature, the patient was treated with conventional induction AML therapy, followed by radiotherapy. This choice, so far, has proved to be a successful strategy, since the patient has shown no signs of relapse after 3-year follow-up.

In conclusion, the current study highlights certain interesting features of GS. Firstly, the negative reactivity for MPO in the current case suggested the diagnosis of a poorly differentiated GS with a poor prognosis. Thus, the patient was assigned to a multidisciplinary protocol of close follow-up for the high risk of relapse. Secondly, since the rhinopharynx is involved in a variety of malignant neoplasms, immunohistochemistry is required for the diagnosis of GS, particularly for the undifferentiated forms, as in the present case. Indeed, it is not uncommon for GS to be misdiagnosed as lymphoma. Finally, a combination of detailed clinical, radiographic and serological work-ups, in association with a thorough histological assessment, is essential to establish the correct diagnosis (29).

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