

## Case Report

# Intracranial granulocytic sarcoma: two cases and literature review

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**Abstract:** Intracranial granulocytic sarcoma was a relatively rare tumor composed of myeloid blasts and/or immature myeloid cells in an extramedullary site which is associated with acute/chronic myeloid leukemia. In this paper, two cases of intracranial granulocytic sarcoma, one male aged 36 and one 28-year-old female, were reported to improve the diagnosis and treatment of such diseases. Diagnostic and treatment procedures for them were retrospectively summarized and relevant literature reviews were combined. Pathological biopsy was conducted to validate the diagnosis. Surgical resections in combination with chemotherapy were performed. The differential diagnosis of intracranial granulocytic sarcoma from malignant lymphomas and alternative small round cell malignancy was confirmed by biopsy and immunohistochemistry.

**Keywords:** Granulocytic sarcoma, extramedullary tumor, leukemia, immunohistochemistry, chemotherapy

## Introduction

Granulocytic sarcoma (GS) is a rare extramedullary tumor consisting of undifferentiated cells. According to statistics, the morbidity rate of GS was approximately 0.7/1000000 in children, and 2/1000000 in adults [1]. It constantly involved with skin, bone, head and neck soft tissues and lymph nodes, but the involvement with intracranial nervous system was extremely rare [2]. Although it has been categorized as the central nervous system tumor by World Health Organization (WHO) in 2007, intracranial GS has been rarely reported in actual clinical work. It has been generally acknowledged that intracranial GS was the intracranial solid manifestation of extramedullary tumor. However, the underlying mechanism, clinical manifestations and effective treatment have been largely unknown. In this paper, we retrospectively analyzed the clinical symptoms, diagnosis and treatment of two cases of intracranial nervous system GS from 2008 to 2013 and reviewed relevant literatures.

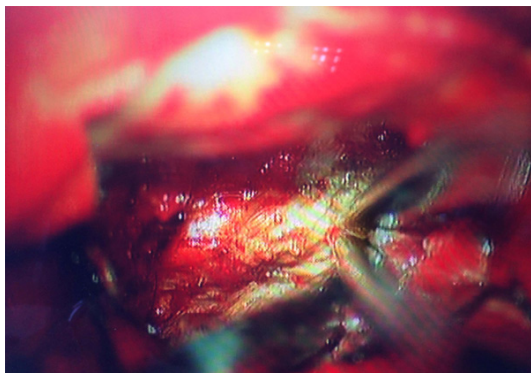
## Case report

### Case 1

A 36-year-old male was admitted to XXX hospital with right facial paralysis for over 3

months and headache for over 10 days. Previous CT and magnetic resonance imaging (MRI) of the head detected space-occupying lesions at the right cerebellopontine angle and inflammation was considered. Upon admission, the patient had a clear mind with equally large and round pupils and the reflex to light. Peripheral facial paralysis was noted at the right side, bilateral pharyngeal reflexes were present, the muscular strength of four limbs was grade V and bilateral Babinski's sign (-) was noted. Repeated MRI of the head revealed the space-occupying lesions at the area of right cerebellopontine angle, which invaded into the jugular foramen and mastoid process. The lesions presented remarkable enhancement with "chaplet-shape" and heterogeneous texture, highly suspected as inflammation. Laboratory examination: WBC was  $7.27 \times 10^9/l$ , the percentage of neutrophils was 52.6%, and the mean width of platelet distribution was normal. He had a history of acute promyelocytic leukemia for 3 years and received standard treatment at a local hospital (regimen unknown). Currently, he was at the remission phase. After admission, he was given antibiotic therapies, ceftriaxone sodium 4.0g IV Qd. After 2-week administration, MRI of the head MR detected no changes in lesion volume. He received

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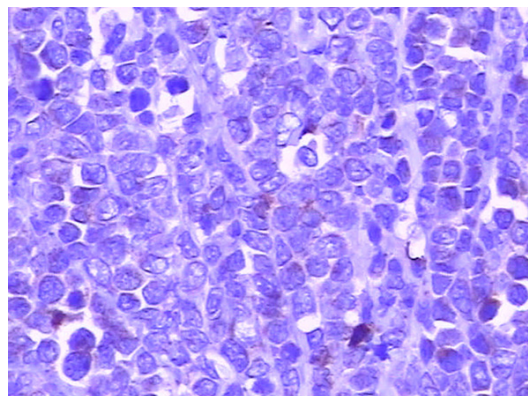


**Figure 1.** Intraoperative photograph showing the appearance of the intracranial GS.

multiple lumbar punctures to isolate cerebrospinal fluid and neither tumor cell nor heterocyst was seen. Craniotomy was subsequently performed via the right retrosigmoid approach for brain exploration. Intraoperatively, white tumor with tough texture fully occupied the right cerebellopontine angle cistern, closely adhered to the cranial nerves and invaded into the petrosal part of temporal bone (**Figure 1**). The blood supply of the tumor was not rich and the tumor margin was unclear. Histopathological findings considered that the tumor was derived from the blood system. Postoperative pathological examination: immunohistochemistry: LCA (-), CD3 (+) in scattered pattern, CD20 (+) in scattered pattern, CD68 (+), SYN (-), MyoD1 (-), CD43 (+), CD99 (+), NSE (-), Lyso (-), S-100 (-), CD56 (-) and LCA (-). Thus, the patient was suspected with GS. At postoperative two weeks, the patient had episodes of headache, vomiting and bucking. Enhanced MRI found that the original tumor became obviously enlarged. He underwent bone puncture and no sign of leukemia relapse was noted. Then, the patient was given chemotherapy (DA regimen) after the tumor at the right cerebellopontine angle was shrank significantly. Until now, he has been followed up for 3 months and is still alive without recurrence.

### Case 2

A 28-year old woman was admitted due to transient absence seizure for over 1 month. Previous MRI of the head indicated space-occupying lesions in the temporal bone and the signs of inflammation were noted. Physical examination revealed the same findings to case 1. She had a history of acute myelogenous leu-



**Figure 2.** HE staining revealing cells with large cell body, abundant cytoplasm and irregular-shape nucleus. Nucleolus could be noted. Small lymphocytes were distributed in a disperse pattern ( $\times 400$ ).

kemia (M2) for 8 years and was treated at a local hospital (regimen unknown). She was at the remission phase. Enhanced MRI revealed the heterogeneous space-occupying lesions in “chaplet-shape” at the temporal bone and invaded into the mastoid process. Infection was highly considered. Multiple lumbar punctures detected no tumor cell or heterocyst in the cerebrospinal fluid. Subsequently, she was delivered with antibiotic therapy of ceftriaxone sodium 4.0g IV Qd. After 2-week therapy, repeated MRI of the head MR found the lesion size was remarkably enlarged. Then, she underwent craniotomy for exploration under general anesthesia via the left subtemporal approach. During the operation, white tumor with tough texture and blurry border was documented. Postoperative pathological examination: LCA (-), CD3 (+ in scattered pattern, CD20 (+ in scattered pattern), CD68 (+), SYN (-), MyoD1 (-), CD43 (+), NSE (-), Lyso (-), S-100 (-), CD56 (-) and LCA(-). GS was considered (**Figure 2**). Postoperatively, the patient received radiotherapy (DA regimen) and whole brain and local IMRT at Hematology of Chinese Academy of Medical Sciences. During 1-year follow-up, no tumor recurrence was noted. She could live an independent life.

### Discussion

GS was first found by Burns in 1811, and named as “leukochloroma” by King in 1853 because the tumor was green due to the presence of myeloperoxidase (MPO). The color of tumor varies according to the content of MPO.

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Approximately 30% of the tumors are not green [3]. In 1966, Rappaport named it as GS with main manifestations of soft tissue lump, which could occur in any organ, especially in the pericardial site. The two patients described in this article developed tumors inside the skull. For one patient, the tumor was located at the area right cerebellopontine angle and at the temporal regions for the other patient. Such disease has been rarely reported during the previous 5 years. The incidence of GS in the leukemia population is not high with a morbidity of approximately 5% in adults and 13% in children [4]. The incidence of intracranial GS has yet to be investigated by large population-based studies.

The pathogenesis of intracranial GS has been elusive. Some scholars believe that the leukemia cells infiltrate into topical vessels, induce cell proliferation locally and form the solid mass, leading to the incidence of extramedullary leukemia [5]. In addition, it has been recognized that intracranial GS derives from hematogenous dissemination. Especially, when the density of peripheral leukocytes  $> 100 \times 10^9/L$ , the phenomenon of severe leukostasis can be observed [6]. The leukemia cells adhere to and destroy the vessel wall, and proliferate locally to form solid GS [7]. Another potential mechanism is that leukemia cells invade into adjacent dura mater through bone marrow, then enter the subarachnoid cavity and V-R gap, and even migrate into the cerebral parenchyma along with vascular gap [7, 8]. In the two cases of this report, the tumors invaded into the dura mater and the subarachnoid cavity but failed to infiltrate into the cerebral parenchyma. No tumor cells were detected in the cerebrospinal fluid. Routine examination upon admission revealed no increase in the count of peripheral blood leukocytes, no abnormality in the classification, distribution and morphology of blood leukocytes and no signs of leukostasis. Regarding the underlying mechanism, the hypothesis that the tumor originates from bone marrow, subsequently invades into the dura mater and subarachnoid cavity is supported. From the anatomical and embryonic perspectives, the irregular bones in the cranial base are predilection sites of intracranial GS, which is supported by the findings of two patients reported in this investigation. However, multiple detections of the cerebrospinal fluid revealed no tumor cells, which is inconsistent with the findings reported

in other literatures. Therefore, the pathogenesis of intracranial GS remains to be further investigated by large sample size studies.

Pathological biopsy has been considered as the gold standard in the diagnosis of intracranial GS. Imaging manifestations of intracranial GS are non-specific including cerebral parenchymal infiltration, intracranial tumor and cerebrospinal invasion, etc. [9]. Although combined use of CT and MRI enhances the accuracy of GS diagnosis, it is a challenging task to make a definite diagnosis due to clinical experience and professional knowledge of the physicians. During the last decade, the application of immunohistochemistry technique has significantly improved the differential diagnosis of GS. MPO has been regarded as one of the pivotal markers of GS due to high sensitivity and specificity to myeloid cells. However, the positive expression rate of MPO varies according to the GS types (i.e. the differentiation degree of myeloid cells). CD68 is expressed within immature myeloid cells, especially the differentiated monocytes. Therefore, MPO and CD68 are not expressed in all GS cases. CD34, as an antigen related to hematopoietic precursor cells, serves as a specific marker of hematopoietic stem cells. However, the expression of CD34 is down-regulated and weakened along with the maturation and differentiation of hematopoietic cells, only expressed in 1/3 of GS patients. CD34 is expressed in almost all AML-M0 and M1 and a majority of M6 and M7 cases. Since CD34 is expressed in 75% patients diagnosed with pre-B cell acute lymphoblastic leukemia (ALL), it is recommended to combine with the expression of TdT, CD3 and CD20 for comprehensive evaluation. Patients are advised to receive peripheral blood and bone marrow examination. For non-leukemic GS patients, special attention should be paid to the morphological and immunophenotype analysis. Combined analysis of medical history, immunophenotype characteristics and cell morphology is able to identify the differentiation of myeloid cells and validate the diagnosis [10].

After the diagnosis is confirmed and the operation is performed, radiotherapy combined with chemotherapy has been regarded as the optimal treatment of GS [11]. However, the selection of therapeutic plans may greatly vary according to the differences in relevant symptoms, tumor sites, the medical history of leuke-

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mia and patients' demographic data, such as age and general conditions.

Chemotherapy combined with radiotherapy is employed to treat solitary intracranial GS without the medical history of leukemia. Solitary intracranial GS may evolve into systemic leukemia that invades into the myeloid system with mean progression time of 5-49 months [12]. Occasionally, GS is used as an index reflecting the transformation from chronic myelopathy into acute myeloblastic leukemia [13]. Radiotherapy or surgical resection alone could alleviate local symptoms rather than improve clinical prognosis or prevent the progression into leukemia [14]. Instead, chemotherapy could remarkably reduce the risk of progressing into leukemia and prolong patients' survival time. Tsimberidou et al. demonstrated that combined use of radiotherapy and chemotherapy prevented the progression into acute myeloblastic leukemia in 21 non-leukemic GS patients [12].

In this report, the two patients were both at the remission phase of acute myeloblastic leukemia. The male patient did not receive the radiotherapy due to poor physical conditions. Following chemotherapy alone, he was followed up for 3 years and the GS did not recur. The female patient underwent chemotherapy in combination with radiotherapy and high clinical efficacy was achieved.

It has been accepted that intracranial GS is sensitive to radiotherapy [7]. The selection of radiotherapy mode mainly depends on the size, site and quantity of tumor, expected survival time of patients and the presence of extracranial diseases. For the intracranial tumor with a diameter of less than 3 cm, stereotactic radiosurgery (SRS) or fractionated SRS can be applied because they can provide better local radiation, reduce radiation injuries and lower the risk of decreases in neurocognitive ability, and it is more efficacious especially for those with long expected survival time. In this study, the tumor size exceeded 3 cm. Hence, SRS was not adopted in either participant. Instead, local conformal IMRT was performed, which could substantially increase the tumor dosage, enhanced the control rate of intracranial GS and prevented adjacent tissues from radiation injury [15]. Mehta et al. [16] recommended that, for multiple intracranial lesions, the appli-

cation of whole brain radiotherapy and local IMRT could achieve good local control and markedly lower the relapse rate. One patient in this report developed a relatively large tumor and the risk of cerebral parenchyma cannot be excluded. Hence, the whole brain radiotherapy and local IMRT were adopted to obtain high clinical efficacy and no tumor recurrence was documented.

Although intracranial GS has been reported, patients with intracranial GS, followed up for 20 and 21 months after corresponding treatment, as enrolled in this study, have been rarely been documented yet [17, 18]. However, the optimal diagnosis and treatment remain to be explored by larger sampling size investigations.

### Disclosure of conflict of interest

None.

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