

Case Report

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Bilateral parotid gland enlargement as a presenting manifestation of relapsed pediatric acute myeloid leukemia

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Abstract

Parotid gland involvement is a rare presentation of Acute Myeloid Leukemia (AML). We report a 10-year-old girl of acute myelomonocytic leukemia with normal cytogenetics and positivity for inversion 16, who after completion of first consolidation of the BFM 2004 AML protocol, presented with bilateral parotid gland enlargement. Bone marrow examination was suggestive of a relapse. Fine needle aspiration of the parotid gland showed presence of myeloblasts. Patient was given FLAG-IDA chemotherapy, with which the parotid swellings rapidly regressed and she achieved a remission and was planned for allogeneic bone marrow transplantation. Acute myelomonocytic and monoblastic leukemias are known to be associated with tissue infiltration. However, exocrine gland involvement such as parotid enlargement is rare and is associated with a poor prognosis as was seen in our patient who despite having inversion 16 positivity had poor disease outcome.

Keywords: acute myeloid leukemia; parotid gland enlargement; granulocytic sarcoma.

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Introduction

Acute Myeloid Leukemia (AML) in children accounts for a very small number of cases, incidence being 2-3 per 100,000 per annum [1]. The prevalence of relapsed AML in children is 24-40% [2]. Acute myelomonocytic (AML-M4) and monoblastic leukemia (AML-M5) are known causes for tissue infiltration. Moreover, exocrine gland involvement such as parotid enlargement is very rare. Parotid gland enlargement presenting as a Granulocytic Sarcoma (GS) / Myeloid Sarcoma (MS) in relapsed pediatric AML is rarely reported. We report a case of a relapsed pediatric AML with bilateral parotid enlargement.

Case report

A 10-year old girl of AML-M4 with normal cytogenetics and positivity for inversion 16 (inv (16)) presented with isolated bilateral, painless parotid gland enlargement (Figure 1a) 26 days after completion of the 1st consolidation of the BFM 2004 AML protocol. There was no fever, organomegaly, evidence of any

cranial nerve palsy including facial nerve palsy or CNS involvement. Her haemoglobin was 11.6 g/dL, Total Leucocyte Count was $11.7 \times 10^6/L$, and platelet count was $63 \times 10^9/L$. Though our first differential diagnosis was mumps, but the absence of fever, pain, and tenderness of the parotid glands, prompted us to investigate for any relapse of the disease. Bone marrow examination confirmed a relapse with presence of 80-90% myeloblasts. Fine needle aspiration of the parotids showed presence of myeloblasts (Figure 1b). CSF examination did not reveal presence of any malignant cells. *KIT* mutation analysis was done and found to be negative. Patient was given 1st cycle of FLAG-IDA chemotherapy, with which the parotid swellings rapidly regressed in size and a remission was achieved. An HLA typing of the family was performed and a 10/10 match was identified in her brother. While the family was arranging finances for the transplant, a second course of FLAG-IDA chemotherapy was administered. However, within a month following the second course she relapsed, this time with complaints of decreased vi-

sion in the left eye with diplopia. Physical examination revealed recurrence of the bilateral parotid enlargement and left lateral rectus palsy. CSF cytology was positive for malignant cells. The patient's family opted for no further therapy and thereafter were lost to follow up.



Figure 1: Bilateral parotid gland enlargement as a presentation of relapse.

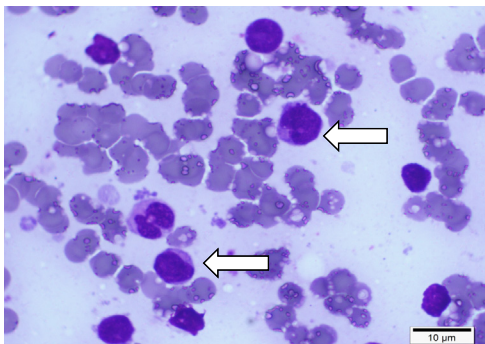


Figure 1b: FNA of the parotid showing myeloblasts.

Discussion

Both AML- M4 and M5 are known to be associated with tissue infiltration in the form of swollen gums, myeloid sarcomas, and skin nodules [8]. However, parotid enlargement is very rare. Myeloid Sarcoma (MS) is composed of myeloblasts, occurring in extramedullary sites in AML. It is more common in the pediatric age group with an incidence of up to 30% in some studies of pediatric AML patients versus 2–5% in adults [3]. It can be present both at the time of initial diagnosis of AML as well as at the time of disease recurrence [4]. Common sites are bone, periosteum, soft tissues, lymph nodes, and skin, but have also been reported in the gastrointestinal tract, testes, breast, cervix, vagina, salivary glands, mediastinum, pleura, and peritoneum. Neiman *et al* reviewed 61 biopsies of MS and only 1 patient had salivary gland involvement [5]. In a case series of 131 patients with MS, most common site was lymph node followed by skin. The rare sites were bladder, breast, thyroid, and pancreas, but none of the patients had parotid involvement [6]. Majority of patients

in these studies were adults. In a case series by Claerhout *et al*, one case each of CNS and orbital MS have been described in pediatric patients [7]. However, no case of parotid MS as seen in our patient was described.

In adults, parotid gland involvement as a presenting manifestation has been reported in newly diagnosed AML [12], newly diagnosed T-cell leukemia [13], and lymphoma [14]. Parotid gland enlargement as the presenting manifestation of pediatric AML is even rarer, with only a few case reports. Geetha *et al* reported a case of a 14-year-old girl with bilateral parotid gland enlargement as initial manifestation of AML [9]. Naithani *et al* reported a case of left side parotid gland enlargement in a newly diagnosed pediatric AML [8]. Both these cases expired during their treatment.

The parotid gland has been described as a site of extramedullary relapse in adults with Acute Lymphoblastic Leukemia (ALL) and AML [10,11]. Parotid gland has been a sanctuary site for relapsed acute leukemia either in isolation or in association with central nervous system [9,15]. Factors predisposing extramedullary relapse in AML include an abnormal karyotype (e.g., t(8;21), inv(16) and t(11q23)), FAB type M4, M5 morphologies, and strong male predominance [16,17].

KIT gene mutations in adult and pediatric AML patients with t(8;21) and in adult AML patients with inv(16) have been associated with a poorer prognosis than in those without *KIT* gene mutations. However, the frequency and clinical impact of *KIT* gene mutations in pediatric AML patients with inv(16) remain unknown. Pediatric AML patients with inv(16) have been reported to represent 3.4% to 6% of the total number of pediatric AML patients [18]. Thus, the number of pediatric AML patients with *KIT* mutations is likely to be very small. Although our patient had favorable inv(16) mutation and did not demonstrate *KIT* mutations, her disease relapsed, and she demonstrated parotid enlargement as extramedullary disease. Further, she became refractory to chemotherapy and developed CNS involvement also.

Recently, Caraffini *et al*, described RAF Kinase Inhibitor Protein (RKIP) as a negative regulator of RAS-MAPK/ERK signaling. A somatic loss of RKIP has recently been described as a frequent event in AML [19]. It has been shown to be associated with monocytic AML phenotypes and proven to be of functional relevance for leukemogenesis. They demonstrated that RKIP is indeed involved in the tissue infiltration of leukemic blasts and, consequently, in the formation of MS. However, this testing was not done in our patient at that time. It is likely that in the future, further such molecular markers would be discovered which could explain poor clinical outcomes in pediatric patients with inv(16) AML.

Conclusion

To conclude, bilateral parotid enlargement as a presenting manifestation of relapsed childhood AML has not been reported, but our case demonstrates that if present should prompt investigations for relapse of AML. Such patients have a poor prognosis as also highlighted by our case who despite having inv(16) and absence of *KIT* mutations had a chemotherapy resistant disease. Newer molecular mutations could be unveiled soon explaining the poor prognosis in pediatric patients of AML with inv(16) mutation.

Conflict of interest: The authors of this manuscript have no conflicts of interest to declare.

Author contribution: All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, A.G., and P.C.; Methodology, A.G, S.N.; Investigation, P.C, S.Y; Formal Analysis, A.G, P.C.; Resources, S.Y.; Writing - Original Draft, A.G, P.C.; Writing - Review & Editing, A.G, S.N.; Visualization, A.G.; Supervision, A.G.

Data availability statement: Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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