



Case report

A sinister mixed phenotype acute leukemia mimicking tonsil lymphoma

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ABSTRACT

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Introduction: Unilateral tonsillar hypertrophy with accompanying cervical lymphadenopathy gives immediate suspicion of lymphoma or squamous cell carcinoma as the most probable diagnosis.

Aim: We aim to highlight the role of diagnostic tonsillectomy for intact looking tonsil as opposed to incisional biopsy for obvious fungating mass or ulcerative lesion. We also emphasise not to overlook abnormal preliminary blood work up. If leukocytosis is present, a peripheral blood film must be done to rule out ongoing infection or a more cynical haematological disease.

Case study: We report a case of a young female presenting with progressive dysphagia as well as bilateral neck swelling. Examination showed a unilateral tonsillar hypertrophy with bilateral cervical lymph nodes highly suggestive of tonsil lymphoma.

Results and discussion: She was opted for tonsillectomy for both diagnostic as well as therapeutic purposes. Histopathological examination (HPE) of the left tonsil removed paired with an elaborated blood workup finally diagnosed her with a rare case of mixed phenotype acute leukemia.

Conclusions: A multidisciplinary team approach and early intervention are crucial to arrive at the correct diagnosis allowing prompt treatment and better prognosis and symptomatic relief.

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1. INTRODUCTION

Acute leukemia is commonly classified into acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL). AML is the commonest type in adults and are typically fatal within months or even weeks if delayed treatment. They usually present with unexplained continuous fever, easy fatigability, loss of appetite and weight, gum swelling and/or some with paraneoplastic manifestations (i.e. skin – leukemia cutis). ALL are more seen in children and may present with lymphadenopathies, testicular swelling, mediastinal mass, or cranial nerve palsies. Mixed phenotype acute leukemia (MPAL) is a rare subgroup and is characterized by having antigens of more than a single lineage. The leukemic blasts can share B/T/myeloid lineages.^{1,2} As it is rare and diagnostic criteria are still lacking, therefore it is difficult to determine any distinct characteristics and the best treatment regimen.² To date, there has been no reported cases presenting as dysphagia with unilateral tonsillar hypertrophy (UTH). UTH with compressive symptoms and/or preexisting risk factors are known to be a red flag for malignancy and are commonly subjected for either diagnostic tonsillectomy or incisional biopsy. This reflects the incidence rate for malignancies especially in the adults.^{3,4} Yalon et al. in 2007 discovered that among 20 000 cases who had undergone tonsillectomy since 1978, 6 of whom were actually diagnosed lymphoma had apparent UTH during their first visit, with or without other accompanying symptoms.³

2. AIM

Here we report a case of a left UTH who was submitted for a diagnostic tonsillectomy to diagnose lymphoma but surprisingly confirmed to be a rare case of MPAL.

3. CASE STUDY

A 22-year-old female presented with 3 months of progressive dysphagia associated with foreign body sensation and was only tolerating soft diet. She later developed a muffled voice as well as multiple painless swellings on both sides of the neck which were increasing in number and size. She denied any fever or night sweats and despite no loss of appetite she lost 3 kg over a month blaming it on poor oral intake. On examination, she was comfortable without any stridor. Intraoral examination showed no trismus or halitosis however had left unilateral tonsil hypertrophy which had an intact surface with multiple crypts but no ulcerating lesion, fungating mass nor exudates (Figure 1a). There was no medialization of the left parapharyngeal wall, nor bulging of the peritonsillar area. The rest of the oral examination was unremarkable. Neck examination showed palpable lymph nodes bilaterally at the posterior triangle with largest measuring 3 × 3 cm at left level Va (Figure 1b), which were firm-rubbery, non-tender and fixed with no skin changes. No nodes palpable over the axilla or the inguinal regions

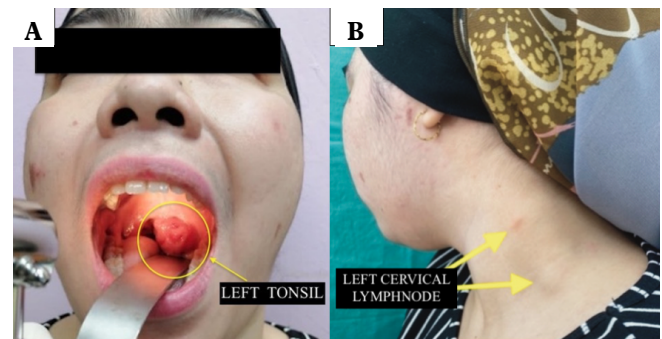


Figure 1. (A) Left unilateral tonsillar hypertrophy (Grade IV) with tonsillar crypts and an intact mucosa; (B) left neck swelling at level Va and Vb.

and no presence of hepatosplenomegaly. Flexible nasopharyngolaryngoscopy (FNPLS) showed that the nasopharynx and supralaryngeal structures were normal.

The blood workup noted leukocytosis $20.5 \times 10^9/L$ on full blood count (FBC) with normal haemoglobin 14 g/dL, platelet level $397 \times 10^9/L$ with raised lactate dehydrogenase to 758 U/L. In view of the suspicious left tonsil, she was subjected to a tonsillectomy to establish the diagnosis as well as to open the upper airways and relieve the symptom of dysphagia. Peripheral blood film (PBF) taken showed consistent leukocytosis with 42% abnormal mononuclear cells. Bone marrow aspiration (BMA) and trephine (BMAT) biopsy, flow cytometry immunophenotyping was performed for further workup and both revealed an unexpected result of mixed phenotype of acute leukemia of T/myeloid subtype (Figure 2). The histopathological examination of the left tonsil ultimately confirmed the diagnosis with the discovery of infiltration of the leukemic cells into the tonsils. The tonsillar tissue was effaced by mixed phenotypic blastoid cells (Figure 2a). The blast cells exhibiting immunopositivity towards leucocyte common antigen (LCA), T cell markers; CD3 (Figure 2b), CD5, CD7, immature markers; CD34 (Figure 2c), TdT, CD99 and myeloid markers; myeloperoxidase (MPO) (Figure 2d) and lysosomal associated membrane protein 1 (LAMP-1). B cell markers, CD20 and CD79a are negative. Ki-67 proliferation index is about 80%. A final diagnosis of secondary infiltration of the tonsil by leukemic cells of MPAL (T/myeloid) was rendered. Two weeks post-surgery, she was tolerating orally well with no dysphagia and the wound site well healed. The diagnosis was explained to the patient, and she was referred to our peers in the haemato-oncology team for further counselling and treatment. She was prescribed with chemotherapy regime hyper-CVAD odd and even for 4 pairs but prior to therapy induction, she was diagnosed with lower limb deep vein thrombosis and was treated with anti-coagulants before finally commencing the chemotherapy. She is currently on her third pair and had overcome a few obstacles such as neutropenic sepsis with candidemia, Covid-19 infection, hospital acquired pneumonia and an infected peripherally inserted central catheter (PICC). She has found a match for an allograft transplant, but the donor is currently pregnant and awaiting to deliver the baby first. BMA post 2nd pair showed pancytopenia with occasional blast cells. She is tolerating orally well with no dysphagia and no recurrence of tonsillar hypertrophy.

4. RESULTS AND DISCUSSION

Asymmetrical UTH is not uncommon and does not necessarily require removal while those who do undergo tonsillectomy are mostly done for therapeutic purposes in cases of recurrent tonsillitis, peritonsillar abscess or for relieving obstructive symptoms caused by bilateral tonsillar hypertrophy (i.e., obstructive sleep apnoea). Another absolute indication is for diagnosis in cases of suspected malignancy.^{3,4} Those presenting with an apparent UTH complaining of either dysphagia, foreign body sensation in the throat, halitosis, muffled voice, or stertor especially with the presence of cervical lymphadenopathy are suggestive of malignancy until proven otherwise. Other probable, but less likely differentials can be chronic tonsillitis, a tonsillolith, or even a tonsil cyst.

Lymphoma represents a complex group of lymphoreticular system malignancies and is among the most common neoplasm after squamous cell carcinoma (SCC) within the head and neck area.^{5,6} The Waldeyer ring (pharyngeal lymphoid ring) is the most frequently identified extranodal head and neck site for lymphoma accounting for 36%–67% occurrences,⁶ where tonsils are the commonest site followed by nasopharynx and base of tongue.^{5,7} It is the most likely differential for tonsil malignancy aside from SCC.^{4,6,8} Non-Hodgkin's lymphoma is more commonly seen compared to Hodgkin's lymphoma within this region and it also accounts for 85% of malignant UTH.⁸ A 10 year review of tonsillar lymphoma by Mohammadianpanah et al, found that commonest subtypes were the diffuse B-cell lymphoma followed by small cell lymphoma, immunoblastic lymphoma and finally anaplastic large cell lymphoma.⁵ Tonsil lymphomas are initially painless with no apparent lesions as the tumour usually invades inwardly creating a submucosal mass. Patients usually seek medical attention at a localized stage I or II with initial complaints of dysphagia with or without other symptoms like cervical lymphadenopathy.⁶

Tonsillectomy is warranted as excisional biopsy is needed to confirm cell lineage, subtyping and ultimately to establish the treatment of choice.^{4,8} As treatment for lymphoma is non-surgical hence no pre-operative biopsy or staging is required prior to tonsillectomy. Meanwhile, SCC in comparison, with pre-existing suggestive features of fungating or ulcerative mass, a deep incisional biopsy (i.e., punch biopsy) of the lesion is adequate for the purpose of pre-operative diagnosis. Diagnostic tonsillectomy is not commonly done for SCC as it will cause difficulty in judging the margins of the remaining tumour for definitive surgical treatment, either open or transoral.⁷ Therefore, tissue diagnosis is first established followed by the staging of disease and treatment allocation. Locally advanced disease with the presence of distant metastasis is non-operable therefore tonsillectomy might cause more harm than good although taking a larger chunk of tissue during the biopsy itself may be helpful in temporarily relieving obstructive symptoms but achieves nothing oncologically.⁷ As all signs pointed towards tonsil lymphoma, discovering a case of MPAL was quite unexpected.

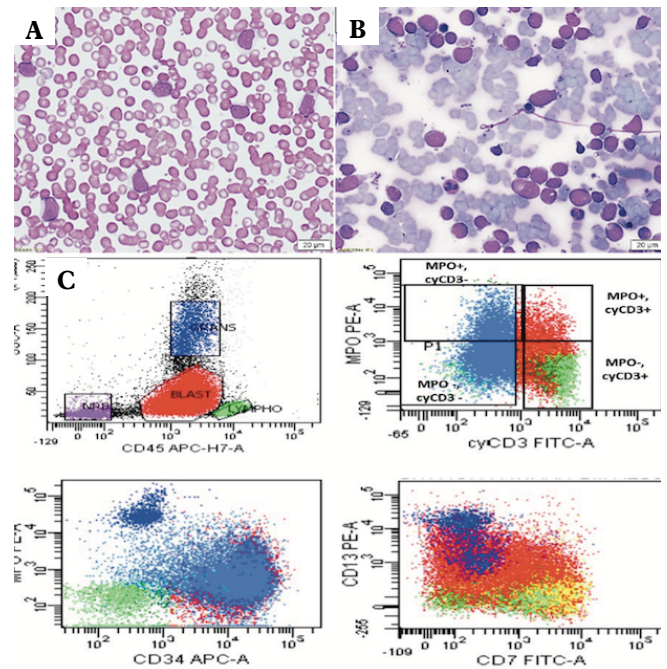


Figure 2. (A) Peripheral blood film showed leucocytosis with many circulating large abnormal mononuclear cells with abundant agranular cytoplasm, irregular nuclei outline and clumping chromatin and occasional with blastoid appearance (magnification $\times 40$); (B) Bone marrow aspirate showed numerous with two population of blast cells (large and small to moderate in size) with scanty cytoplasm, very high nucleus cytoplasmic ratio and open chromatin pattern (magnification $\times 40$); (C) Flow cytometry immunophenotyping showed the blast (dim to intermediate CD45, CD34 positive) expressed both myeloid (MPO, CD13) and T cell markers (cyCD3, CD7) with few other myeloid and T cell markers (not shown in the figure) which consistent with mixed phenotype acute leukaemia (T/myeloid).

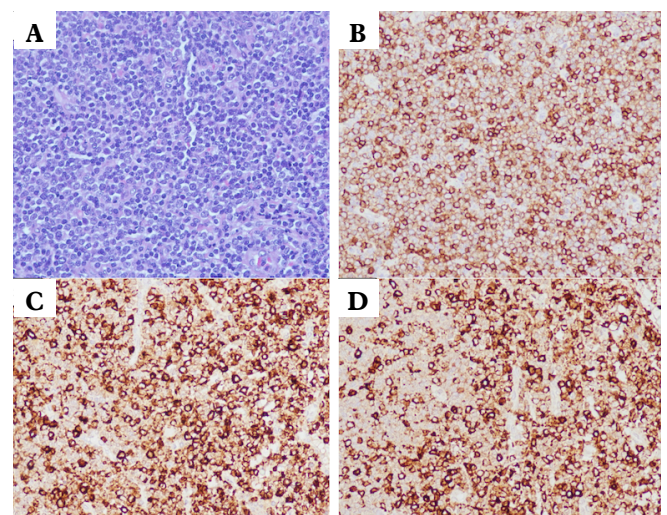


Figure 3. (A) Haematoxylin and eosin show effacement of tonsillar architecture by infiltration of malignant blastoid cells (HE stain, magnification $\times 400$); (B) The blastoid cells exhibiting positive co-expression towards immunohistochemistry staining for CD3, CD34 (C) and MPO (D) (magnification $\times 400$).

MPAL is a rare type of acute leukemia that accounts for about 1%–5% of all leukaemias.⁹ Historically it has been labelled by various names including mixed lineage leukaemia, bilineal leukaemia and biphenotypic leukaemia.¹⁰ The WHO has proposed a simplified diagnostic algorithm to define MPAL, influenced by fewer and more lineage-specific markers. Myeloid lineage requires the presence of myeloperoxidase as detected by immunohistochemistry, flow cytometry or cytochemistry or any evidence of monocytic differentiation. It needs at least 2 positive markers from either non-specific esterase cytochemistry, CD11c, CD14, or CD64CF. The B lineage requires multiple antigens like CD19, CD79a, CD22 and CD10 while T lineage can be seen with cytoplasmic or surface CD3 as intense as background reactive T-cells.^{9,10} All possible combinations can be observed including B/myeloid, T/myeloid, B/T or even rarely B/T/myeloid. Revision of the WHO classification in 2016 states that in cases with 2 distinct blast populations, each of them should meet criteria for either B-lymphoblastic leukaemia (B-ALL), T-ALL or AML.⁹⁹

Patients with MPAL will commonly present like other acute leukaemias which is fatigue, infections, bleeding disorders and with a high blast count.^{10,11} Wang et al. reported in 2015 of extramedullary presentation of the disease with cervical lymphadenopathy which later on during the illness developed generalized lymphadenopathy.¹² Similarly, in 2016, Monabati et al. reported a case presented with cervical and axillary lymphadenopathy associated with malaise and weakness.¹³ It has yet to be reported of a patient complaining of dysphagia, muffled voice accompanied with findings of an apparent UTH and posterior neck cervical lymphadenopathy. Although the patient was only taking soft diet and lost weight over the course of illness, she had no obvious fatigability or other B symptoms. All the findings had strongly suggested a case of tonsil lymphoma in which tonsillectomy was strongly indicated.

As of now, there are no set therapy nor any prospective trials for MPAL, but aggressive chemotherapy is commonly prescribed to eradicate specific types of leukemic cells.^{9–11} In 2015, Wolach et al. had suggested for those with T positive MPAL to add on tyrosine kinase inhibitor to the treatment while non-T MPAL is treated with an ALL regimen combined with an allogeneic stem cell transplant.^{10,11} Some institutions had come up with studies comparing the outcome of MPAL patients with a matched control of ALL and AML groups and results showed a worse outcome of the two. Retrospective trials reported median overall survival to range from 14.8 to 18.0 months, while the rate to achieve long term survival is less than 20%. This series also suggested that MPAL had the complete remission rate and is better with an ALL therapy or and ALL/AML combined regimen than with AML-type therapy.¹⁰

5. CONCLUSIONS

- (1) Apparent UTH with obstructive symptoms and cervical lymphadenopathy is an ominous sign for malignancy.
- (2) Decision for either tonsillectomy or incisional biopsy depends on the clinical appearance of the tonsils.

- (3) Surgery may be done for therapeutic purposes (relieve obstructive symptoms).
- (4) MPAL is a rare type of acute leukemia and may present with tonsillar hypertrophy.
- (5) Multidisciplinary approach is crucial to not delay diagnosis and treatment.

Conflict of interest

None declared.

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Ethics

The patient has given the informed consent for publication of the image, and all parts of the image are anonymized.

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