Molecular and oral manifestations of langerhans cell histiocytosis preceding acute myeloid leukemia

Qi Zhang1†, Xiaoting Wu2†, Xiaobo Wang1, Evenki Pan3 and Li Ying4*

Abstract

Background: Langerhans cell histiocytosis (LCH) is a heterogeneous neoplastic disorder that is rarely seen in patients aged 60 years and older. It is reported that elderly patients with LCH have a higher chance of having malignancies. In the oral cavity, patients with LCH can present with mucosal ulcers and extensive osteolysis, making it difficult for clinicians to make a proper diagnosis.

Case presentation: We reported an 82-year-old Chinese woman with oral symptoms as the first presentation of LCH, and eventually developed acute myeloid leukemia (AML). She suffered diffuse ulcers involving the entire gingival mucosa and the left half hard palate, and had lost several teeth. Genomic DNA sequencing of the cells from LCH revealed multiple mutations in TET2, BRAF, SRSF2, NRAS, MAP2K4 and so on. The patient declined the BRAFV600E inhibitor (Vemurafenib). Although a dramatic improvement of the oral ulcers was achieved after symptomatic treatment, the patient developed acute myeloid leukemia (AML) and died.

Conclusions: This report presented the diagnostic difficulties of LCH with oral manifestations and highlighted the importance of radiological assessments and laboratory tests. Moreover, many of the mutations detected in our LCH patient are frequently seen in AML, suggesting that AML and LCH cells in this patient share the same origin.

Keywords: Histiocytosis, Langerhans-cell, Leukemia, Mutation, Case reports

Background

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasm, it is rarely diagnosed in adults (1–2 per million adults per year), even fewer in people over 60 years of age [1]. The clinical presentations are highly heterogeneous, ranging from a solitary lesion to multisystem involvement that is associated with organ dysfunction, which can affect the bones, skin, lungs and hematopoietic system, etc. Patients with oral LCH can present as mucosal ulcers, gingival hyperplasia, jaw necrosis, and dental luxation or loss [2]. These clinical manifestations are difficult to distinguish from those of periodontitis or gingivitis. Definitive diagnosis can be made after histopathological examination.

The constitutive activation of the mitogen-activated protein kinase (MAPK) pathway is the hallmark of LCH, making it a target of therapeutic agents [3]. The current understanding is that LCH are likely arises from the abnormal differentiation or recruitment of hematopoietic precursors, supporting the hypothesis that LCH is the result of misguided myeloid differentiation [4]. It is reported that LCH can occur before or after, or concurrent with myeloid neoplasms such as acute myeloid leukemia (AML), suggesting the two entities are clonally...
related [5]. The unclear etiopathogenesis and wide clinical spectrum pose great challenges to diagnosis, treatment and prognosis. We herein reported a unique case of LCH in which the patient first presented with oral ulcers and later developed AML. Genomic mutations in the LCH cells were studied and discussed.

**Case presentation**

An 82 year-old woman presented to our clinic complaining of severe oral ulcerations that caused difficulty eating. Intraoral examination showed diffuse ulcers with suppurative discharge involving the entire gingival mucosa and the left half hard palate, multiple teeth were lost (Fig. 1a).

A biopsy was performed, pathology showed an intense proliferation of histiocytes and significant infiltration of eosinophils and lymphocytes (Fig. 1b). CD-1a, S-100 and CD163 were highlighted on immunohistochemistry staining (Fig. 1c–e). Bone destruction was found by oral and maxillofacial radiology (Fig. 2a), and hip magnetic resonance imaging (MRI) revealed inhomogeneous signal intensity at pelvic bones, lumbosacral vertebrae and bilateral femurs (Fig. 2b). A blood count showed WBC leucocytes $7.85 \times 10^9/L$, RBC $3.3 \times 10^{12}/L$, hemoglobin 112 g/L and platelets $175 \times 10^9/L$. A bone marrow biopsy was performed, flow cytometry identified slight developmental anomaly in primitive myeloid cell with increased monocytes (21.01%), there was granulocyte dysplasia. The diagnosis of LCH with myelodysplastic syndrome (MDS) was made. Genomic sequencing was performed in the LCH cells, which revealed mutations in TET2, BRAF, SRSF2, NRAS, MAP2K4, MPL, DDX41, and MSH3 (Table 1).

The patient declined chemotherapy or $BRAF^{V600E}$ inhibitor (Vemurafenib), she was treated with dexamethasone mouth rinse, thalidomide (100 mg/day) and prednisone (30 mg/day). One month later, a dramatic improvement of the oral ulcers was achieved, and the patient could eat normally (Fig. 1f). Thalidomide and prednisone were tapered. However, three months later, she developed bone ache, fatigue, and shortness of breath. The blood routine examination was performed: WBC $74.04 \times 10^9/L$, RBC $2.98 \times 10^{12}/L$, hemoglobin 92 g/L, platelets $10 \times 10^9/L$. There was significant increase of myeloblasts and promonocytes in the peripheral blood and the bone marrow (Fig. 2c–d), consistent with the development of AML. The patient decided to pursue comfort care and expired a month later.

**Discussion and conclusion**

The clinical features of oral LCH are mainly swelling, pain, mucosal ulceration, and gingival hyperplasia, and tooth loss [2]. Oral soft tissue lesions usually occur in conjunction with jaw lesions, which affect the alveolar bone and lend to dental luxation or loss. In addition, LCH can mimic the clinical symptoms of other conditions, including viral infection, malignancy, periodontal and granulomatous diseases [4]. Differentiating LCH from these is challenging and a dentist may miss the
underlying diagnosis. In the oral cavity, patients with LCH occasionally present with painful mucosal ulcers and dental loss, which may be misdiagnosed as periodontitis. Positive immunohistochemical stains of CD-1a and S-100 are the characteristic biomarkers of LCH. Definitive diagnosis can be made after careful radiological and histopathological examination. Although patients with oral LCH have limited oral lesions, they are at risk of systemic involvement [6]. Therefore, once a patient has been diagnosed with LCH, a thorough physical
| Gene | Amino acid change | Coding | Exon | Variant effect | Allele frequency | Transcript | Locus | Protein change | MIM number | Clinical significance | Phenotype |
|------|------------------|--------|------|----------------|------------------|------------|-------|----------------|------------|---------------------|-----------|
| TET2 | p.Q1540*         | c.4618C>T | 11   | Truncated mutation | 40.5           | NM_001127208.3 | –     | –              | 612,839    | Likely oncogenic     | Chronic Myelomonocytic Leukemia, Myelodysplastic Syndromes, Angioimmunoblastic T-Cell Lymphoma |
| TET2 | p.R131Kfs*5      | c.391dup | 3    | Frameshift mutation | 28.6           | NM_001127208.3 | –     | –              | 612,839    | Likely oncogenic     | –         |
| BRAF | p.V600E          | c.1799T>A | 15   | Missense mutation | 17.0           | NM_004333.6  | chr7:140,753,335 | V600E      | 164,757 | Oncogenic | Anaplastic Thyroid Cancer, Colorectal Cancer, Melanoma, Non-Small Cell Lung Cancer, Biliary Tract Cancer, Glioma, Astrocytoma, Leukemia |
| SRSF2 | p.P95H           | c.284C>A | 1    | Missense mutation | 3.2            | NM_001195427.2 | –     | –              | 600,813    | Oncogenic | Acute Myeloid Leukemia |
| NRAS | p.G12D           | c.35G>A | 2    | Missense mutation | 0.8            | NM_002524.5  | chr1:114,716,126 | G12D       | 164,790 | Oncogenic | Colorectal Cancer, Erdheim-Chester Disease, Langerhans Cell Histiocytosis, Rosai-Dorfman Disease, Histiocytosis, Melanoma, Thyroid Cancer |
| MAP2K4 | p.R145W        | c.433C>T | 5    | Missense mutation | 3.2            | NM_003010.4  | –     | –              | 601,335    | Unknown | – |
| MPL  | p.W632C         | c.1896G>C | 12   | Missense mutation | 5.0            | NM_005373.3  | –     | –              | 159,530    | Unknown | Myelofibrosis with myeloid metaplasia, Thrombocytopenia 2, Amegakaryocytic Thrombocytopenia |
| DDX41 | p.R311Q        | c.932G>A | 9    | Missense mutation | 1.1            | NM_016222.4  | –     | –              | 608,170    | Unknown | Myeloproliferative/ lymphoproliferative Neoplasms |
| MSH3 | p.H781Y         | c.2341C>T | 17   | Missense mutation | 15.6           | NM_002439.5  | chr5:80,778,742 | H781Y      | 600,887 | Unknown | Endometrial Carcinoma, Familial Adenomatous Polyposis 4 |
examination should be performed to rule out other diseases, especially malignancies. Therefore, it is necessary to perform radiological assessment and a tissue biopsy to ensure the diagnostic accuracy, LCH has been mainly diagnosed in children, rarely in adults, even fewer in people over 60 years of age.

It has been observed that adult patients with LCH have a higher incidence of malignancies, the exposure to chemotherapeutic agents such as etoposide has been thought to have contributed to the carcinogenesis [7]. However, our patient did not receive such agents for LCH treatment, but still developed AML. Consistent with that, about 32% of adult LCH patients who had not received etoposide were diagnosed with secondary malignancies, including solid tumors, lymphomas, and hematologic malignancies, arguing other causes [1]. which indicated the occurrence of malignancy in patients with LCH has irrelevance to its treatment, but the mechanism of the association between adult LCH and malignancy has not been elucidated. In this report, the gene mutations in the clonal evolution of the patient deserved consideration.

On the one hand, some mutations related with MAP kinase (such as BRAF, MAP2K4, NRAS) were found in our patient (Table 1). BRAF, an intracellular kinase, is frequently mutated in melanoma, thyroid and lung cancers among others. The variant residue at sequence position 600 in this protein is a glutamic acid which has a negatively charged side chain, making it hydrophilic. BRAFV600E mutation is a constitutive activator of the MAPK pathway that promotes cell proliferation, apoptosis and invasion by activating the downstream MEK-ERK transduction pathway, which is involved in more than 50% of LCH lesions [8, 9]. Besides, MPL and MAP2K4 mutations can also activate MAPK and/or PI3K/AKT signaling pathways and promote malignant transformation [10, 11]. MPL, a transmembrane protein receptor, is frequently mutated in myeloproliferative neoplasms including essential thrombocytosis and AML [10]. The variant residue at sequence position 632 is a cysteine which has a side chain capable of forming a disulfide bond with another cysteine, and hence provide a strong structural support for the protein. MAP2K4 is a tumor suppressor and intracellular kinase that has been reported to be associated with histiocytic neoplasms [11]. The variant residue at sequence position 145 in this protein is a tryptophan which has an aromatic side chain. Of note, Zhang J et al. [12] found another MAPK (MAP3K15) gene mutation in a girl who developed acute lymphoblastic leukemia after LCH, and they suggested that MAPK gene may be a potential biomarker for the conversion of LCH to hematological malignancies, which was consistent with our findings. In addition, N/KRAS mutation detected in histiocytic neoplasms were also seen in myeloid leukaemias, suggesting the common hematopoietic stem/progenitor cells they shared [13]. This mutation is closely associated with myeloblast development and could be the predictor of evolution to clonally relevant haematological malignancies [4, 13]. Hence, genomic sequencing analysis of patients with histiocytosis is helpful in clarifying the staging and providing positive early intervention [12, 13]. The patient also had a mutation in DDX41 gene, which is associated with myeloid neoplasm including MDS, AML and CMML, but rarely with LCH [14].

On the other hand, some mutations related to epigenetic regulation (such as TET2, SRSF2) were also found (Table 1), most of them have been described to participate in the pathogenesis of AML. The residue at sequence position 1540 and 131 in TET2 protein were altered and these variants may be closely related to the development of hematologic malignancies. SRSF2 is an RNA splicing factor that is frequently mutated in hematological malignancies, and its variant residue is a histidine with a positively charged side chain, making it hydrophilic. It was reported that SRSF2 and TET2 mutations were detected in LCH cells of a patient with concurrent mixed histiocytosis and acute myelomonocytic leukemia (AMML), it showed that TET2 mutation could occur before BRAF and SRSF2 mutations in vitro [15]. MDS patients with SRSF2 mutation had inferior 5 year overall survival than those without that, leading to a faster evolution into AML [16]. Yoshimi A reported that co-mutations in SRSF2 and IDH2 can drive myeloid malignancy development through promoting lethal myelodysplasia in vivo [17] and revealed a pathogenic cross-talk between the epigenome and RNA splicing in AML. These findings also suggest that mutations in AML are not isolated.

Two-hit hypothesis supports that the occurrence of AML is a multi-step process consisting of a wide range of genetic and phenotypic changes [18]. Generally, mutations as the first-hit do not directly give rise to AML, the coordination with order with other mutations made the transformation into a full-blown AML eventually. Lindsey et al. [19] have analyzed eight specific gene mutations related to secondary AML (s-AML) and found the most frequent were ASXL1 and SRSF2 mutations which occurred at 32% and 20% frequency, respectively. As for the order in which mutations appear, many researchers supported those gene mutations involving DNA methylation, chromatin modification, and RNA splicing appear before others, followed by transcription related, while mutations associated with the tyrosine kinases and RAS signaling pathways are often the last event in clonal evolution [17]. What’s more, there are some reports on the mutual transformation of LCH and AML, in which researchers have proposed that this concomitant was
owing to the common tumour hematopoietic stem cell they shared, but the specific genetic machinery was inconclusive [2]. In our case, the presence of TET2, BRAF, SRSF2, NRAS, MAP2K4, MPL, DDX41, MSH3 mutations might provide an explanation for the clonal evolution of LCH and AML: TET2 mutation as the first-hit appeared first, the subsequent BRAF and NRAS mutations initiated the occurrence of LCH and MDS, finally the SRSF2 mutation and the former together drove an AML transformation (Fig. 2e).

In conclusion, this report described an elderly female with oral symptoms as the first presentation of LCH, and eventually developed AML. We highlighted the necessity of radiological and histopathological examinations in the diagnosis of oral LCH, and the importance of genetic testing for early intervention, early treatment and management of LCH patient. Moreover, the mutation profiles suggest that LCH and AML might have a common clonal origin, and provided hypothesis of the development of LCH and AML.

Abbreviations
LCH: Langerhans cell histiocytosis; MDS: Myelodysplastic syndrome; AML: Acute myeloid leukemia; AMML: Acute myelomonocytic leukemia.

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Author contributions
All authors contributed to this report concept and design. QZ and XTW wrote the first draft of the manuscript, XBW performed the treatment, EP performed the gene analysis, and LY collected relevant clinical data and critically revised the article. All authors read and approved the final manuscript.

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Not applicable.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Second Hospital of Dalian Medical University.

Consent for publication
Written consent to publish this information was obtained from the participants' legal guardian/next of kin.

Competing interests
The authors declare that they have no competing interests.

Author details
1Department of Hematology, The Second Hospital of Dalian Medical University, Dalian, China. 2The Third Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, China. 3Nanjing Geneseeq Technology Inc., Nanjing, China. 4Department of Gastroenterology, The Second Hospital of Dalian Medical University, Dalian, China.

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