A case report and literature review of GLI1-altered soft tissue tumours

伊利沙伯醫院
QUEEN ELIZABETH HOSPITAL

Dr. Jenny LK Tse, Dr. Joshua HY Ng

Department of Pathology, Queen Elizabeth Hospital/Pamela Youde Nethersole Eastern Hospital

Introduction

GLI1-altered soft tissue tumours are rare soft tissue neoplasms, which are characterized by GLI1 gene fusions or amplifications. This entity has been recently included in the WHO Classification of Tumours, Head and Neck Tumours (5th Ed.). In this case report, we present a case of this uncommon neoplasm in a 13 year-old Chinese male presenting with a tongue mass. The diagnosis was confirmed with molecular studies. The literature review of this entity will provide insights on its clinical presentation, histological features, immunohistochemical profile, molecular characteristics and prognosis.

Case report

A 13-year old Chinese male presented with a non-healing wound and an underlying firm mass measuring 1.5 cm at the left anterior tongue. The mass persisted for months and caused discomfort for the patient. An excisional biopsy was performed for histological examination.

Histological examination showed tongue tissue with multilobulated tumour growth, located mainly in the skeletal muscle level. It consisted of nests and sheets of tumour cells with rich delicate fibrovascular network separated by anastomosing fibrous stroma. The border of the tumour was partially circumscribed with focal infiltration. The tumour cells were epithelioid to ovoid. They possessed variable eosinophilic to pale vacuolated cytoplasm, round to oval nuclei, open chromatin and distinct nucleoli. Protrusion of tumour cells in vascular space was observed. Mitotic count was up to 7 mitotic figures per 10 high power fields. Ki67 index was around 10%. No necrosis was present. The tumour focally entrapped minor salivary glands and ducts at the periphery. The overlying squamous epithelium was unremarkable.

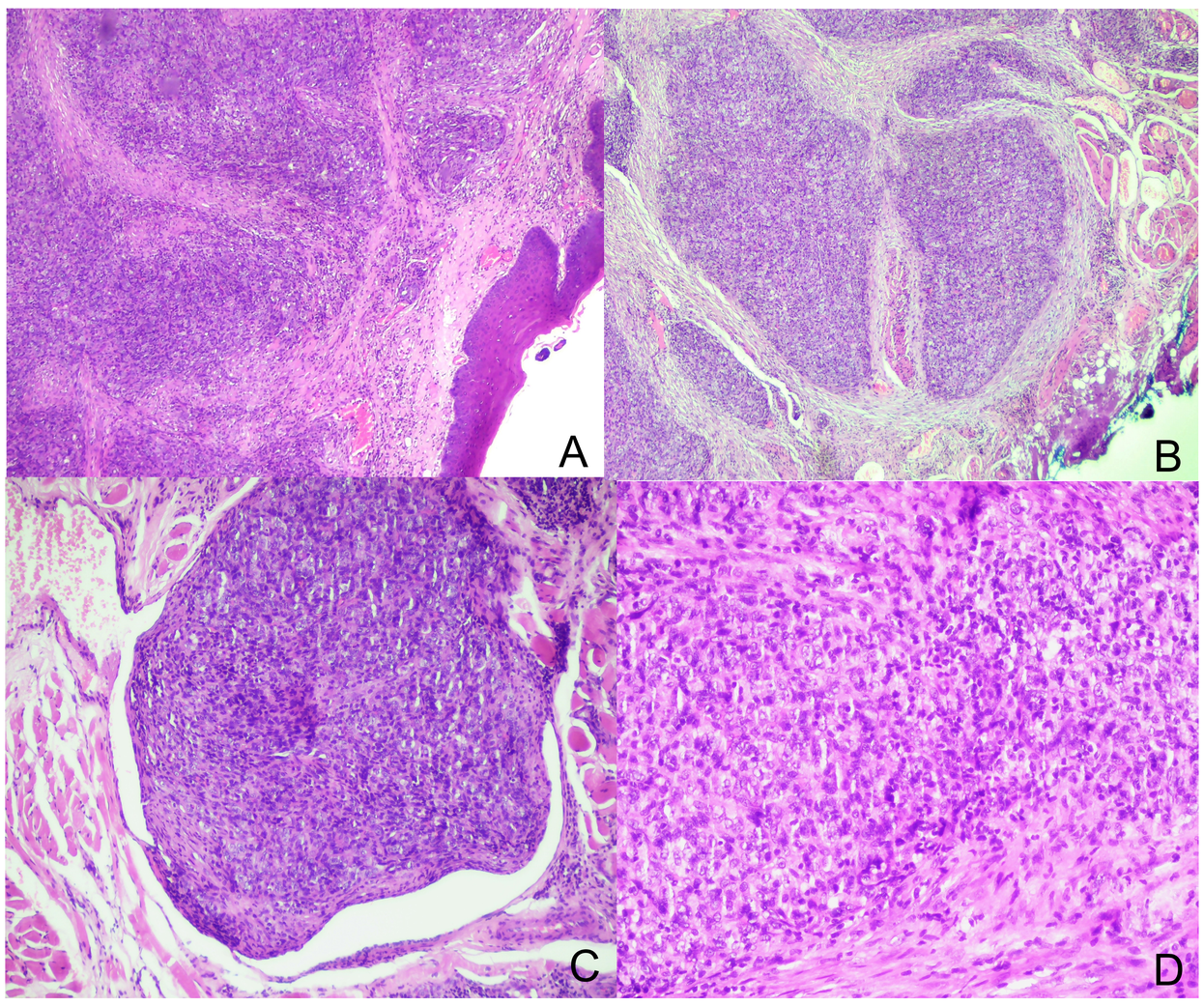

Figure 1. GLI-1 altered soft tissue tumour of tongue on H&E staining. A and B, Tongue tissue with multilobulated tumour growth, consisting nests and sheets of tumour cells with rich delicate fibrovascular network separated by anastomosing fibrous stroma. The overlying squamous epithelium was unremarkable (A). The tumour nests were deep to the skeletal muscle layer (B). C, Protrusion of tumour cells in vascular space. D, Epithelioid to ovoid tumour cells with variable eosinophilic to pale vacuolated cytoplasm, round to oval nuclei, open chromatin and small distinct nucleoli.

A panel of immunohistochemical studies was performed with the following results:

- positive for CDK4 and CD56
- weak focal staining for GATA3, S100, SOX10, CD10, CD68, synaptophysin and CD99
- preserved INI-1
- negative for AE1/AE3, EMA, chromogranin, CK8/18, p63, p40, 34βE12, desmin, SMA, c-kit, myogenin, GFAP, ERG, HMB45, CD34 and STAT6.

Fluorescence in-situ hybridization for MDM2 gene amplification was positive. GLI-1 translocation with high level amplification of the translocated segment (5' end of the break-apart probe) was detected by fluorescence in-situ hybridization.

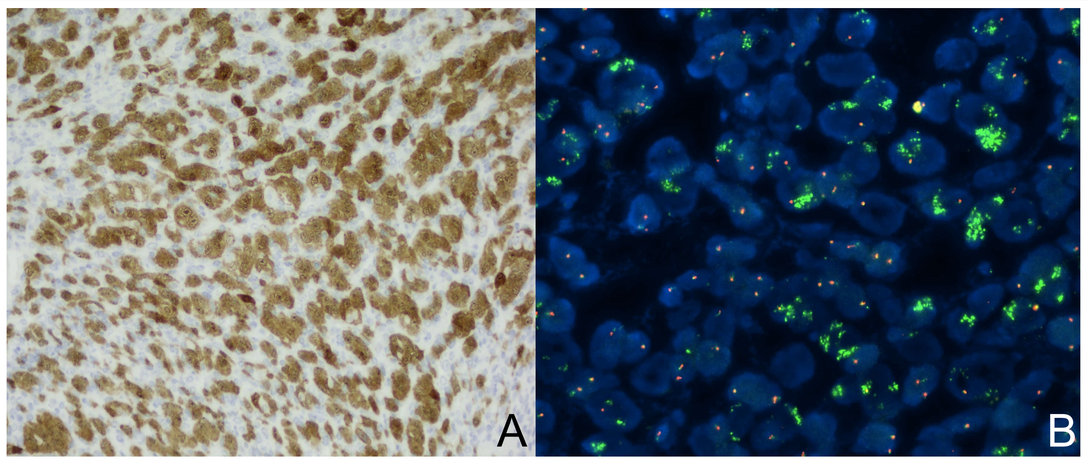

Figure 2. A, Positive immunostaining for CDK4 among tumour cells. B, FISH showed GLI-1 translocation with high level amplification of the translocated segment.

After excisional biopsy, there was a 1 cm residual mass around the scar. Left partial glossectomy was performed to excise the residual tumour with clear margin. Neck dissection was performed, which showed no evidence of lymph node metastasis. No recurrence or distant metastasis was noted up till now.

Discussion and literature review

GLI1 is an important transcription factor downstream the Hedgehog signaling pathway. Its abnormal activation is closely associated with the development, behaviour and prognosis of tumours. Our reported case was the third case harboring both GLI1 translocation and amplification from the 71 previously reported cases.

Considering other molecular-related findings, clinical presentation, histological features and immunohistochemical findings, our case showed compatible features of this rare entity. GLI1-altered soft tissue tumours occur over a wide age range (from 1-88 years) with the tongue being one of the most common sites of involvement in the head and neck region (19/29 cases, including our case). Other reported sites in the head and neck region include submandibular soft tissue, neck, soft palate, floor of mouth, mandibular gingiva, tonsil and oropharynx. Patients typically present with a slow growing painless mass. Macroscopically, they are circumscribed lesions that can be solid or cystic. Similar to our case, tumours frequently show multilobulated growth microscopically. Tumour protrusion into surrounding vascular spaces is a common feature. The cytological features are non-specific; tumour cells can be epithelioid to ovoid to spindled, with round to ovoid nuclei, pin-point nucleoli and variable amount of eosinophilic to clear cytoplasm. Mitotic activity and necrosis can be present or absent.

Immunohistochemically, GLI1-altered soft tissue tumours have non-specific immunoprofile, although most cases in the reported series showed CD56 positivity with variable S100 expression. Additional focal or patchy staining for SMA, AE1/AE3 and CD10 were observed in some cases. Due to close proximity of genes, coamplification of STAT6, CDK4 and/or MDM2 could occur and be detected by immunohistochemistry or molecular studies. Our case also showed coamplification of CDK4 and MDM2, as supported by positive immunostaining and fluorescence in-situ hybridization respectively.

The biological behavior of GLI1-altered soft tissue tumours is variable. Among the 46 cases reported with available follow-up information (including our case), 6 cases developed local recurrences, 5 cases with regional lymph node metastasis and 8 cases with distant metastasis. The presence of high mitotic index may reflect the chance of aggressive behaviour, as 6 of the 8 cases with distant metastasis had a mitotic count of >=5/10HPFs. Tumour necrosis was also present in some of these cases. No relationship between the subtypes of GLI1 alterations and metastasis was identified.

Conclusion

Our case of GLI1-altered soft tissue tumour in the tongue in a 13-year old Chinese male additionally expanded the preexisting series of 71 cases reported. Our case was the third case showing both GLI1 translocation and amplification, and showed compatible clinical features in terms of tumour site and presentation as a painless mass. Histologically, the tumour showed multilobulated growth, rich delicate fibrovascular network and epithelioid to ovoid tumour cells with vascular protrusion. Immunohistochemical studies showed positive CD56 and CDK4 staining. This case demonstrated the importance of molecular analysis in the diagnosis of mesenchymal tumours with non-specific histological features and immunoprofile. Further research study is needed to understand the molecular biology in the tumourigenesis of GLI-1 altered soft tissue tumours, which will guide potential use of immunostain as surrogate marker in tumour diagnosis and the development of targeted therapy of this rare entity.

References

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