Date of meeting: Valencia May 25th-28th2022

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Case number: B-1978335
Material distributed: 1, H&E slide distributed of 3rdbiopsy

Low-grade fibromyxoid sarcoma of orbit, recurrences

Clinical History:
A 17 year old young lady presented with a slowly progressive proptosis of right eyeball for months without history of trauma, fever, pain, nor general disease.Vision is normal, optic nerve oedema grade 1. CT/MRI shows a lobulated nodular intraconal mass in right orbit, of 25mm diameter. The mass is iso-intense on T1 and slight hyperintense on T2, homogeneous contrast with gadolinium. RX and Clinical congruent with cavernous malformation or hemangioma.
Surgery was planned for excision with Tisseel, during operation the initial diagnosed was doubted and attempted to remove the whole lesion; the mass had a firm consistency no blood pooling and synechia with globus, optic nerve and apex; complete removal was attempted but abolished for fear of harm to optic nerve,
After final diagnosis 4 months later a complete excision of the lesion was planned, however not succeeded. The mass was only partially encapsuled with a thin layer. Therefor a large exenteration with eyelids, sinus maxillaris and ductus lachrymalis was performed in a 3rd surgery.
2 years later she is without any recurrences and is coping psychologically relatively well, with wearing an epithese

Pathology: Histology:

Biopsy 1: 5 small pieces of an infiltrating orbital mass: 24-10-2018
Clinical diagnosis; lymphangioma, with intra-lesional injection of Tisseel
Macroscopy biopsy 1:4 formol fixated, soft, elastic glassy substances 13-8-5mm maximum.
Microscopy biopsy 1:orbital fragments buildup ofmyxoid matrix in with spindle shaped cells with few cytoplasm and bland nuclei; no signs of atypia or pleiomorphism. In this matrix multiple small vessels with normal appearance.
Immuno-staining: CD 34 and CD99 positive in all matrix cells and vessels. CD 68 only few dispersed histiocytes. S100, alfa SMA, EMA, Caldesmon negative. Ki 67 max 1%+. Stat 6 -. MUC4 + in spindle cells.
Molecular genetic test:Fish: regions/genes LSI FUS (DC BA) (16p11) and LSI EWSE1 (DC BA) (22q12) not above the threshold of 10% the sample was not good evaluable, negative for gen rearrangements
Biopsy 2: growth of known orbital mass: 11-03-2019
Macroscopy biopsy 2: The second samplewas a lobular, beige, soft tissue sample 32-30-20mm, surrounded by a thin white capsule.

Microscopy biopsy 2: same appearance a biopsy 1: myxoid matrix with slender spindle cells and plump quiet nuclei without atypia or pleomorphism. Multiple small vessels and few lymphocytes. Positive section margins. Ki 67 < 5%, extremely rare PHH3 + cell.
Immuno-staining: CD 34 and CD99 positive in all matrix cells and vessels. CD 68 only few dispersed histiocytes. S100, alfa SMA, EMA, Caldesmon negative. Ki 67 max 1%+. Stat 6 -. MUC4 + in spindle cells. MDM2 negative.
Molecular genetic test: Fish: regions/genes LSI FUS (DC BA) (16p11) and LSI EWSE1 (DC BA) (22q12) the sample was good evaluable, negative for gen rearrangements

Biopsy 3: exenteration specimen: 17-06-2019
Macroscopy: orbit 45-45-45mm with eyelids, ductus nasolacrimalis, sinus maxillaris.
Microscopy:multinodular, partially encapsulated, partially infiltrative tumour. Same appearance of myxoid matrix with slender spindle cells, small vessels and lymphocytes. Negative sections margins with smallest margin of at least 0.8mm.
MUC4 negative in section margins,
Biopsy 4: granulation tissue: 04-02-2022
Microscopy: granulation tissue and cicatrisation, markers negative.

Discussion:

This case represents atypical evolution of an extremely rare entity in the orbit, diagnosed as low-grade fybromyxoid sarcoma.

General information concerning soft tissue tumours indicates that benign mesenchymal tumours outnumber sarcomas by a factor 100. The annual clinical incidence of benign tumours of soft tissue is estimated as at least 3000 cases per 1 million population; sarcoma had an incidence of about 50 cases per 1 million inhabitants. Global is that < 1% of all malignant tumours with a higher incidence in children and above 65y old. There are no data to indicate a change in incidence, nor significant geographical differences. A lot of names and definitions have been changed in the last decades after new insides by molecular and genetic analyses of the tissue samples, so better diagnosis, prognosis and treatment. Most tumours arise de novo without any known environmental cause (exception chemical carcinogens, radiation, virus, immune-deficiency and genetic susceptibility). (8)

Soft tissue tumours are classified by the WHO in benign, intermediate (locally aggressive), intermediate (rarely metastasizing) and malignant. Grading in function of mitotic activity and necrosis. New WHO classification of mitosis is per defined surface in mm2 in place of per 10 HPF. Limitations of grading of this kind of tumours is due to theheterogenicity and number of mitosis is not corresponding to local aggressiveness. . Prognosis is most of all linked to the possibility of completeness of removal with large section margins, which if very difficult to impossible in the orbit unless loss of vision and eye.

Low-grade fibromyxoid sarcoma is a malignant fibroblastic neoplasm characterized by alternating collagenous and myxoid matrix and seemingly bland spindle cells with a whorling growth pattern and multiple small blood vessels (1). These tumours consistently have either FUS-CREB3L2 or FUS-CREB3L1, and LSI EWSR1 gene fusions. The hallmark is also a MUC-4 positivity. (7, 9)

The most common sites of involvement are the proximal extremities and trunk, usually subfascial in depth (6). Less common locations include central body sites and superficial soft tissues (later more commonly in children). 20% < 18 years The true incidence is not known and underestimated due to mimicking other sarcomas without and before newer and availability of ancillary diagnostic markers. Very rare cases are described in the orbit, but maybe it is underreported, also because of wrong diagnosis. (2,3,4)

This case represents a typical histologic representation with the typical MUC4 positivity, so very suggestive of LGS . Meningioma can also express MUC4 but the histology and other immune stainings are negative

No known etiology of genetic susceptibility

Pathogenesis: the cytogenetic hallmark of low-grade fibromyxoid sarcoma is the t(7;16)(q33;p11), present in 2/3 of the cases another 25% show supernumerary ring chromosomes (1,7).

Overlap with the entity of sclerosingepitheloidfibrosarcoma is documented, also by the same MUC4 positivity and the same genetic aberrations; the chimeric FUS-CRED3L2 protein functions as an aberrant transcription factor causing deregulated expression of CREB3L2 target genes such as MUC4 (7). The beta subunit is considered as an oncogene.

Conclusion: Low-grade fibromyxoid sarcoma of orbit

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