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Leiomyosarcoma with Isolated Metastasis to the Extraocular Muscle: A Case Report involving Whole-Exome Sequencing

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Case Report

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Abbreviations:
IHC: Immuno Histochemical; MRI: Magnetic Resonance Imaging; NGS: Next-Generation Sequencing; SMA: Smooth Muscle Actin

ABSTRACT

Background: Whole-genome sequencing analysis of leiomyosarcoma of the orbit, a rare condition, has seldom been reported. Here, we describe a case of metastatic orbital leiomyosarcoma, which was confirmed before the diagnosis of the primary tumor.

Case presentation: A 71-year-old man presented with total ptosis of the right eyelid. Limitations of supraduction and infraduction of the right eye were present, resulting in left hypotropia at the primary gaze. Enhanced magnetic resonance imaging of the right orbit revealed an extraconal, peripherally enhancing mass arising from the superior rectus muscle. The diagnosis of leiomyosarcoma was confirmed by histopathologic examination. Next-generation sequencing revealed the absence of mutations such as TP53, RB1, and ATRX, which were previously detected in leiomyosarcoma.

Conclusion: This case indicates that in patients with ocular movement limitation and ptosis, an orbital mass on the external ocular muscle should be considered, along with the possibility of metastatic lesions. Systemic examination and excisional biopsy should be performed.

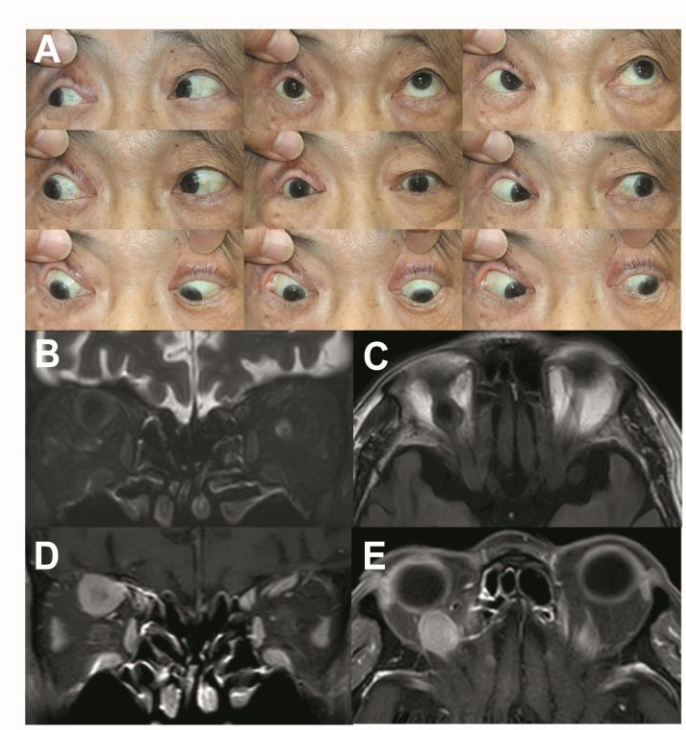
INTRODUCTION

Orbital metastasis is uncommon and occurs in 2%-3% of patients with cancer [1]. It is rarely the initial manifestation of a systemic malignancy. Leiomyosarcoma is a mesenchymal neoplasm that mimics smooth muscle cell differentiation [2]. Leiomyosarcoma of the orbit, metastatic or primary, has rarely been reported [3-5]. Moreover, to our knowledge, the diagnosis and clinical course of metastatic orbital leiomyosarcoma, involving assessments using Next-Generation Sequencing (NGS), have not been reported. Here, we present a case of metastatic leiomyosarcoma, first presenting with symptoms in the orbital area, in which NGS was performed to evaluate common cancer-associated genes.

CASE PRESENTATION

A 71-year-old man presented to the ophthalmology clinic with a 2-week history of blepharoptosis in the right eye (Figure 1).

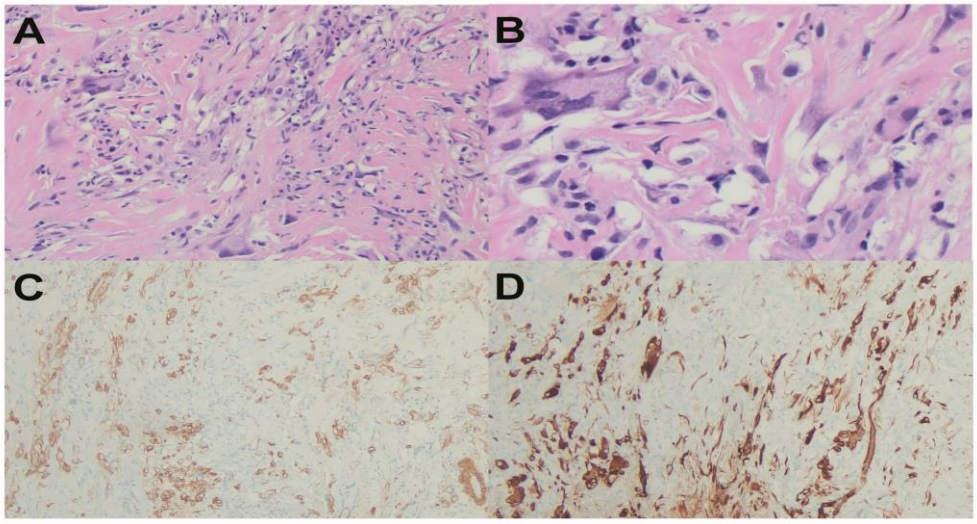
Figure 1. Clinical photograph and orbital magnetic resonance imaging. (A) At presentation, ocular duction and version showed definite limitations of supraduction and infraduction of the right eye. (B) Pre-gadolinium T2-weighted fat suppression Magnetic Resonance Imaging (MRI) shows a right superior rectus mass. (C) Transaxial T2-weighted MRI demonstrates a well-defined 1.6 cm round mass that is margin intermediate signal intensity and internal low signal intensity. (D,E) T1-weighted post-gadolinium MRI demonstrated gadnolinium enhancement of the mass.



His medical history included diabetes mellitus, atrial fibrillation, and hyperlipidemia. He had also undergone a partial colectomy for the removal of a sigmoid tumor, followed by chemotherapy and right nephroureterectomy due to renal cell carcinoma, 9 years ago. Six months before presentation, multiple lung nodules with pleural effusion

were detected, and biopsy revealed anthracitic pigmentation. On ocular examination, the best-corrected visual acuity was 20/25 in the right and 20/30 in the left eye. Margin reflex distance was -5.0 and 3.0 mm in the right and left eyes, respectively. Both pupils were isocoric and round, and the pupillary light reflex was normal. An alternate prism cover test revealed 16 prism diopters of left hypotropia in the primary gaze both at a distance and near fixation. Ductions and versions revealed limitations of supraduction (grade-3) and infraduction (grade-2) in the right eye, whereas no exophthalmos was noted in the left eye. Enhanced orbital Magnetic Resonance Imaging (MRI) revealed an extraconal, well-defined, and enhancing round mass measuring 3.5 cm in maximal diameter arising from the superior rectus muscle. The mass showed spontaneous enhancement without evidence of bone invasion or destruction. Under general anesthesia, we performed superior orbitotomy and biopsy of the extraconal orbital mass. Microscopic pathology revealed the presence of spindle cells, epithelioid cells, and frequent pleomorphic cells, including multinucleated giant cells in fibrotic stroma. Immuno HistoChemical (IHC) staining showed that some spindle and pleomorphic cells were positive for Smooth Muscle Actin (SMA) and desmin, consistent with a malignant smooth muscle neoplasm, and specifically, leiomyosarcoma (Figure 2).

Figure 2. Histopathological examination of the case.



Histopathological examination demonstrated characteristic spindle and pleomorphic cells with abundant eosinophilic cytoplasm, nuclear atypia, indicating leiomyosarcoma. (A, B) Admixed spindle and pleomorphic cells in fibrotic stroma (hematoxylin and eosin staining, magnification 200X and 400X). (C, D) Immunohistochemical staining revealed some tumor cells to be positive for desmin and alpha-smooth muscle actin (magnification 100X). The patient was diagnosed with metastatic orbital leiomyosarcoma with superior rectus invasion. Additional excisional biopsy of the right abdominal wall mass was performed, and the abdominal wall mass was found to be composed of histologically similar cells with severe central fibrosis. The differentiated spindle cells were also positive for SMA and desmin. The tumor was diagnosed as a pleomorphic leiomyosarcoma. Whole-exome sequencing was performed on the formalin-fixed paraffin-embedded tumor tissue using the Illumina HiSeq 2500 platform, with an average read length of 2×10^1 bp, according to manufacturer instructions (Macrogen Inc, Seoul, Republic of Korea). Target region bases were sequenced for each sample using the HiSeq 2500 system (Illumina, San Diego, CA), achieving an average coverage depth of 715X (Macrogen Inc, Seoul, Republic of Korea). After applying a similar filtering method to the exome sequencing data, as done in a previous study [6]. we observed 107

somatic mutations involving 103 genes. Most mutations in each tumor specimen represented single-nucleotide variations (47%), whereas multi-nucleotide variation accounted for 43%, deletions for 6%, and insertions for 5% of the mutations (Table 1).

Table 1. Frequency of somatic mutations in pleomorphic leiomyosarcoma.

Somatic mutations	Frequency
Average coverage	110.91
Covered ≥ 4 reads (%)	99.68
Total variant count[a]	107
Single nucleotide variants (%)	50 (47)
Multi-nucleotide variants (%)	46 (43)
Deletions (%)	6 (6)
Insertions (%)	5 (5)
Mutations per Mb[b]	1.43

Note: [a] Total variant count comprises all variants located in positions with a minimum coverage of six reads and the mutated allele present in at least 2% of the reads, remaining after filtering the sequencing data against 9,977 East Asian individuals from The Genome Aggregation Database v2.1.1, 4,327 East Asian individuals from The Exome Aggregation Consortium v0.3.1, and 1950 in-house control exomes from Korean individuals.

[b] Mutations per Mb was calculated by dividing the total number of somatic mutations by the total number of called nucleotide positions (≥ 6 reads)

TMB=10^7 variants/74.569526 Mbases=1.43 MUT/Mb

In comparison to previous studies, fewer mutations were identified using similar variant calling.TP53, MDM2, CDKN2A, KIT, ATRX, RB1 and MED12 somatic mutations, which were frequently detected in other leiomyosarcoma NGS studies, were not identified [7].The final diagnosis was metastatic leiomyosarcoma, and the patient received one cycle of systemic chemotherapy (adriamycin). The patient received hospice care because of his worsening condition but died due to respiratory failure one month after diagnosis.

DISCUSSION

We report a case of metastatic orbital leiomyosarcoma that was detected without prior identification of the primary tumor. Leiomyosarcomas predominantly arise in the uterine myometrium, but can also appear at other anatomic sites, including the retroperitoneum, upper and lower limbs, epidermis or dermis, and vasculature. Leiomyosarcomas can present as primary or metastatic orbital tumors and as secondary tumors after prior radiation therapy (as seen in patients with a history of retinoblastoma) [4]. Leiomyosarcomas have been observed to metastasize to the orbit from various locations in ten cases, including the spermatic cord, soft tissue of the thigh, rectum, uterus, hip, gastrointestinal tract, abdomen, and veins. Among these previously reported cases, only two have involved extraocular muscle invasion [3-5]. Metastatic orbital leiomyosarcomas demonstrate a more

diffuse enhancement than primary orbital leiomyosarcomas, which are isointense to the extraocular muscle on T1-weighted MRI and have notable peripheral rim enhancement. However, MRI findings of metastatic orbital leiomyosarcoma have varied across cases [8,9]. Our patient presented with a lesion that radiographically appeared intrinsic to the extraocular muscle and had both diffuse enhancement of the lesion but also recognizable rim enhancement.

CONCLUSION

Despite their aggressive nature, little is known about the genetic alterations in leiomyosarcoma. Array and cytogenetic-based studies of leiomyosarcoma have shown significant molecular heterogeneity [10]. With frequent copy number alterations such as loss of chromosomal regions 13q and 10q. Other studies have suggested that alterations in TP53, MDM2, CDKN2A, KIT, ATRX, and MED12 are associated with leiomyosarcoma. Additionally, the germline mutation associated with RetinoBlastoma (RB1) has long been recognized as a risk factor for leiomyosarcoma [11]. The mutation profile of our patient was distinct from those in previous studies as we analyzed a single pleomorphic leiomyosarcoma, instead of an ordinary leiomyosarcoma. Thus, the outcome of our case indicates that the molecular pathway of pleomorphic leiomyosarcoma could be distinguished from that of other leiomyosarcomas. In summary, our case shows that although rare, leiomyosarcoma should be considered in the differential diagnosis of an orbital mass, as metastasis to the orbit can also occur from a retroperitoneal leiomyosarcoma. The results of the whole-exome sequencing indicated the absence of genes that were previously associated with leiomyosarcoma. Further studies of the molecular pathway involved in pleomorphic leiomyosarcomas are needed.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study adhered to the Declaration of Helsinki and the protocol was approved by the Institutional Review Board of Kangwon National University Hospital. The patient consent was obtained with a signed consent form.

CONSENT FOR PUBLICATION

The guidance of patient provided written consent for publication of the patient data and accompanying images in this case report.

AVAILABILITY OF DATA AND MATERIAL

All data generated or analysed during this study are included in this published article.

COMPETING INTEREST

No potential conflict of interest relevant to this article was reported.

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None.

AUTHOR's CONTRIBUTIONS

YJY contributed to data acquisition, data analysis, and manuscript drafting. KYL contributed to design of the work and manuscript revision. All authors read and approved the final manuscript.

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