Review article

Orbital retinoblastoma: present status and future challenges - a review

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ORBITAL RETINOBLASTOMA: PRESENT STATUS AND FUTURE CHALLENGES - A REVIEW.

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ORBITAL RETINOBLASTOMA: PRESENT STATUS AND FUTURE CHALLENGES - A REVIEW.

ABSTRACT

Orbital retinoblastoma is a catastrophic event traditionally carrying a dismal prognosis. Although its incidence is less in the developed countries but continues to be one of the major diagnosis at presentation in the developing world. Orbital retinoblastoma encompasses a wide range of distinct clinical entities with varying tumor load. There are no standard treatment protocols as of now but the current preferred management is multimodal with a combination of initial high-dose chemotherapy, surgery, external beam radiotherapy and prolong chemotherapy for twelve cycles. In spite of progress on all fronts including surgical, medical, diagnostic, genetic and rehabilitative with improving survival rates, however lack of access to medical facilities, lack of education about the need for early medical attention and cultural resistance to enucleation continue to contribute to an epidemic of extra ocular disease at diagnosis in the developing world. This review introduces the various terminologies used in the spectrum of orbital retinoblastoma, discusses in details the clinical aspects and management protocols, current status and the future directions.

Key words
Retinoblastoma
Orbit
Extra ocular
Chemotherapy
Radiotherapy
Proptosis

1. INTRODUCTION

Retinoblastoma is the most common intraocular malignancy in children, with a reported incidence ranging from 1 in 15,000 to 1 in 18,000 live births [1]. It is bilateral in about 25%-35% of cases [2]. The average age at diagnosis is 18 months, unilateral cases being diagnosed at around 24 months and bilateral cases before 12 months [2]. Retinoblastoma was associated with near certain death just over a century ago. Early tumor recognition aided by indirect ophthalmoscopy and refined enucleation technique contributed to an improved survival from 5% in 1896 to 81% in 1967. Advances in external beam radiotherapy in the 1960s and 1970s, resulted in further substantial eye salvage.[2]

The recent advances like identification of genetic mutations, replacement of external beam radiotherapy by chemoreduction as the primary management modality, use of chemoreduction to minimize the size of regression scar with consequent optimization of visual potential, identification of histopathologic high risk features following enucleation and provision of adjuvant therapy to reduce the incidence of systemic metastasis, protocol based management of retinoblastoma

with accidental perforation or intraocular surgery and aggressive multimodal therapy in the management of orbital retinoblastoma have contributed to improved outcomes in terms of better survival, improved eye salvage and potential for optimal visual recovery.

2. PRESENT STATUS

In neglected or untreated cases retinoblastoma can demonstrate extra ocular spread primarily through optic nerve[3] and also through the sclera[4]. Though it is a rare clinical presentation in developed countries ranging from 6.3% to 7.6%[5,6], it is not an unusual feature in developing and under developed world. Leal-Leal C et al[7] reported an incidence of 18% in a large multi-center study from Mexico. Kao LY[8] et al from Taiwan reported the incidence of orbital retinoblastoma to be 36% in a large study. The incidence is even higher around 40% from Nepal where Badhu B et al[9] reported proptosis to be the most common presenting feature of retinoblastoma.

Orbital retinoblastoma is one of the major contributors to mortality and carries a poor prognosis for life.[10-14] The presence of orbital invasion is associated with 10 to 27 times higher risk of metastasis when compared to cases without orbital extension.[15-17]

The 5 year survival rates of orbital retinoblastoma has been reported to be 88% from United Kingdom[18], 91% from Japan[19] and 93% from United States[20,21]. However the mortality in developing countries is still high owing to late presentations compounded by socio-economic factors with the mortality reported as high as 50-90%.[9,14,22,23,24]

3. CLASSIFICATIONS

Orbital retinoblastomas have been variously classified. Childrens Cancer Group (CCG) classification criteria[25] (Table 1) and classification based on the clinicopathological presentations[26] (Table 2) are used.

4. CLINICAL PRESENTATIONS:

4.1 Presenting Age

It is well known that orbital retinoblastomas manifest commonly due to late presentations. The average age at diagnosis is 18 months[2]. In contrast to this Menon et al[27] reported the average age at diagnosis to be 30 months for orbital retinoblastoma whereas Doz et al[28] and Antoneli CB[29] et al reported it as 38 and 32.9 months respectively.

4.2 Most common presenting feature

The most common presenting sign or symptom was leukokoria in the Antoneli[29] series (68%) in comparison to menon[27] series where it was reported to be 72%.

But in the menon[27] series proptosis was the most common presenting sign (83%). The rate of proptosis as the most common presenting sign was 75.9% versus 24.1%, in patients with unilateral and bilateral disease.

4.3 Primary Orbital Retinoblastoma

This refers to a clinically or radiologically detected orbital extension of an intraocular retinoblastoma at the initial presentation, with or without proptosis or a fungating mass. Silent proptosis with manifest intraocular tumor is the usual presentation. (Figures 1a and 1b) Proptosis with inflammation generally indicates reactive sterile orbital cellulitis secondary to intraocular tumor necrosis. Palpable orbital mass (Figure 2) , eyelid swelling or an exuberant fungating orbital mass (Figure 3) are other manifestations.[26]

4.4 Secondary Orbital Retinoblastoma

This refers to orbital recurrence following an uncomplicated enucleation for intraocular retinoblastoma. Orbital recurrence may present between weeks to years after the primary surgery. Unexplained displacement, bulging or extrusion of a previously well fitting conformer or prosthesis is a characteristic finding. Secondary orbital retinoblastomas may also present as a conjunctival nodule.[26] Orbital recurrence of retinoblastoma after enucleation usually carries poor prognosis with reported rates of mortality being as high as 94-100%.[30,31] Distant relapse was found to be the commonest cause of mortality.[31]

4.5 Accidental Orbital Retinoblastoma

This refers to inadvertent perforation, fine needle aspiration biopsy or intraocular surgery in an eye with unsuspected intraocular retinoblastoma[26]

4.6 Overt Orbital Retinoblastoma

This refers to previously unrecognized extrascleral or optic nerve extension discovered during enucleation. A pale pink episcleral nodules or an enlarged and inelastic optic nerve are indicators of overt orbital retinoblastoma that needs to be recognized during enucleation.[26] The prognosis can be dismal if these cases are not managed carefully.

4.7 Microscopic Orbital Retinoblastoma

This refers to retinoblastomas with full thickness scleral infiltration, extrascleral extension or invasion of the optic nerve on histopathologic evaluation of an enucleated eye for intraocular retinoblastoma.(Figure 4) There may not be any clinically evident orbital extension of retinoblastoma.[26] These high risk histopathologic features have a strikingly higher incidence in developing countries as compared to the published data from the developed countries[3,16,17,32,33] as demonstrated by Vemuganti et al.[34] In this series 46% of the 76 eyes enucleated for advance retinoblastoma in India had optic nerve invasion at or beyond lamina cribrosa and 7% had scleral infiltration or extrascleral extension. This could also partly contribute to the high incidence of orbital retinoblastoma in developing countries.

5. INVESTIGATIONS

A careful and detailed evaluation of the patient is mandatory. Apart from the routine clinical work up, regional lymph nodes need to be palpated and a fine needle aspiration biopsy should be done if found to be involved. Imaging modality of choice is MRI of orbits and brain. Alternatively a CT Scan can also be performed to confirm the presence of orbital retinoblastoma.(Figures 5a and 5b) A metastasis work up involves bone marrow biopsy and cerebrospinal fluid cytology. Whole body bone scans using technetium-99 as shown by Kiratli PO et al[35] and Flourine-18 flourodeoxyglucose positron emission tomography (PET CT) as demonstrated by Moll AC et al[36] may pick up early metastasis. Biopsy can be done in those cases where the primary diagnosis or histopathology is unavailable.

6. TREATMENT

6.1 Primary orbital retinoblastoma

There is no proven definitive therapy or management protocols for orbital retinoblastoma. They continue to remain a challenging disease to treat because of its complex nature and usually various combination therapies are needed to achieve reasonable results. White L et al[37] has discussed the use of chemotherapeutic agents including cyclophosphamide , teniposide, cisplatin, vincristine, doxorubicin in conjunction with external beam radiotherapy. Menon et al[27] and Doz et al[28] have shown encouraging results with the use of etoposide in the management protocols. Acquaviva et al[38] favoured combination of chemotherapy with radiotherapy. On the other hand Antonelli[29] showed no benefit from aggressive chemotherapy alone. Goble et al[39] showed good long term survival with multimodal therapy.

6.1.1 Why do we need multimodal therapy ?

a. Systemic chemotherapy alone unlikely to eradicate residual orbital disease[29,40]
b. Orbital exenteration alone unlikely to achieve surgical clearance.[30,31]
c. External beam radiotherapy unlikely to prevent systemic metastasis.[41,42]
d. Histopathologic evidence of viable tumor cells even in phthisical eyes following neoadjuvant chemotherapy.[43]

Based on the current evidence as mentioned above Honavar et al [44] developed a treatment protocol comprising of initial triple drug high dose chemotherapy (3-6 cycles) followed by appropriate surgery, orbital radiotherapy and an additional 12 cycle standard dose chemotherapy. Detailed protocol is listed in Table 3.
In this series six cases of orbital retinoblastoma without intracranial extension and systemic metastasis underwent the protocol as described above and the authors reported dramatic resolution of orbital involvement and a mean event-free survival of 36 months. Most of the eyes following chemotherapy become phthisical.(Figures

6a and 6b) The authors agreed that their encouraging protocol needs validation and further studies are needed to know whether fewer cycles are as equally effective since there are concerns of the long term effects of high dose chemotherapy.

6.2 Secondary orbital retinoblastoma

Hungerford et al[30] and Reese et al[31] have reported dismal results and poor prognosis for cases of orbital recurrences. None of the 25 cases reported by Reese et al survived. Most of the deaths occur within two years. The point to be taken into account in these series was lack of multimodal approach. In contrast Goble et al[39] demonstrated long term survival with local surgical excision, orbital radiotherapy and systemic chemotherapy. Antoneli et al[29] reported encouraging results from multimodal approaches but was not supportive of aggressive chemotherapy. Based on the increasing literature support for a multimodal therapy Honavar et al's[44] proposed protocol (Table 3) is currently under investigation for the management of secondary orbital retinoblastoma with very encouraging early results. However long term results of all the current multimodal protocols need to be reviewed before definite protocols can be formulated in future.

6.3 Accidental orbital retinoblastoma

Eyes with retinoblastoma undergoing enucleation deserves special considerations.[26]

a. All efforts should be taken to prevent accidental perforation.
b. It is preferable to avoid applying traction sutures at the insertion of extra ocular muscles to avoid perforation
c. Hemostats applied to muscle stumps provides adequate traction.
d. Retinoblastoma with sterile orbital cellulitis should be adequately treated to reduce the inflammation before enucleation.

Eyes with retinoblastoma which underwent inadvertent intraocular surgery should be immediately undergo an extended enucleation that additionally includes the conjunctiva overlying the entry points or over the ports with a 4 mm margins all around.[45] In cases where prompt enucleation is not possible all such entry points or ports should be subjected to triple freeze-thaw cryotherapy followed by enucleation as appropriate. All such eyeballs merit special histopathologic analysis for high risk features and specific analysis of the entry wounds for the presence of tumor cells. Metastasis work up in the form of bone marrow biopsy and cerebrospinal fluid analysis for the presence of tumor cells is mandatory. Following enucleation, it is recommended to subject the patients to orbital external beam radiotherapy and 12 cycles of high dose chemotherapy.[45]

6.4 Overt orbital retinoblastoma

Extra ocular extension suspected during surgery deserves special considerations.

a. If an extra-scleral lesion is visible, it should be completely excised along with the overlying tenon's capsule during enucleation.[44]

b. The surgeon should aim at an optic nerve length of 15 mm. In case due to unforeseen circumstances the length of the optic nerve obtained is less than 10 mms when it is suspected to be involved due to increased thickness or inelasticity, Honavar et al[26] preferred to explore the orbit and attempt an additional optic nerve length during the same sitting.
c. Biointegrated implants should be avoided in suspected cases of orbital retinoblastoma as there is possibility of implant exposure due to subsequent external beam radiotherapy.

All cases of overt orbital retinoblastoma undergo metastasis work up in the form of bone marrow biopsy and cerebrospinal fluid analysis for the presence of tumor cells. Following enucleation, it is recommended to subject the patients to orbital external beam radiotherapy and 12 cycles of high dose chemotherapy.[45] Chantada et al[46] in an exclusive study of overt orbital retinoblastoma using a multimodal approach has shown 5 year event free survival rates to be 84% in a group of 15 patients.

6.5 Microscopic orbital retinoblastoma

Several studies have now identified high risk factors for extra ocular recurrences to be post-laminar optic nerve involvement , invasion of optic nerve transection, massive choroidal invasion, scleral infiltration and even anterior chamber involvement.[3,10, 14,17,47,48] The patients where the tumor involved the cut end of optic nerve, scleral or extrascleral involvement are recommended to undergo external beam radiotherapy followed by 12 cycles of high dose chemotherapy.[44]

7. GLIMPSE OF THE FUTURE AND ITS CHALLENGES

When reviewing the literature one fact that stands out clearly is the increasing survival of patients with orbital retinoblastoma. Progress has been made and is continuing on all fronts including surgical, medical, diagnostic, genetic and rehabilitative.[49,50]

Multimodal therapies for advanced retinoblastoma are picking up pace and support from all spheres as amply elucidated in this review. Histopathologic evaluations of eyes following neoadjuvant chemotherapy for orbital retinoblastoma have further vouched for multimodal approaches.[43] The introduction of stem cell rescue along with high dose chemotherapy has added another dimension to the treatment of orbital retinoblastoma.[51,52] The Childrens Oncology Group trials (COG trials) currently undergoing has made a great effort to standardize the treatment protocols worldwide. Their well designed COG ARET 0321 trial of intensive multimodal therapy for extra ocular retinoblastoma will probably lay to rest most of the confusion revolving around management protocols.

Advances in external beam radiotherapy for retinoblastoma with more precise control of the beam through better collimation and tighter isodose curves strongly argues of its continuing supportive role in the management. The modern approaches that are being investigated include stereo tactic conformal radiotherapy using a micromultileaf collimator, proton therapy using a fixed horizontal beam and tantalum localization or a rotating gantry with spot scanning.[53] Better survival has led to increasing research in newer implants with focus on orbital development and hence better cosmesis.

On the diagnostic front exploring the fetal eye is a new frontier. Fetal Magnetic resonance imaging (MRI) and fetal three-dimensional ultrasound are being increasingly explored for prenatal diagnosis. The only two cases reported of in-utero diagnosis using fetal ultrasound had massive extra ocular extension.[54,55] Whole body bone scans using technetium-99 as shown by Kiratli PO et al[35] and Flourine-18 flourodeoxyglucose positron emission tomography (PET CT) as demonstrated by Moll AC et al[36] reflect a glimpse of what possible lies in store for early detection of metastasis.

On the genetic front there has not been a great progress inspite of the fact that RB1 was the first human cancer gene to be cloned. Development of an automated, inexpensive screening examination for RB1 mutations has been a long term need. However recently Parsam VL et al[56] from the authors group have developed and published a combinatorial and less expensive approach for the detection of RB1 mutations which is likely to have applications as a screening tool. Ali MJ et al[57] has for the first time explored the possible correlations between different types of mutations on the RB1 gene and clinical presentations. It is interesting to note that large deletions were found to correlate with extra ocular extension and metastasis at presentation. Further efforts are needed to make it a routine part of patient care.

On the social front awareness through education and outreach to the community has helped to prevent delayed presentations and an early referral. Impact of educational programmes in certain developing nations of Central America where it was linked with the vaccination programmes is continuing to yield encouraging results with the rate of orbital retinoblastoma diagnosis reducing by almost half in the post-campaign period.[58,59] Similar programmes could be cloned to developing countries in Africa and Southern Asia specifically targeting the education of general population and primary care providers.

Lastly other areas being investigated include pharmacologic enhancement of radiotherapy, use of tumor cell targeting techniques, differentiating agents, immunotherapy and employing metastasis suppressor genes to prevent metastasis.[37,60]

8. CONCLUSIONS

Orbital retinoblastoma still stands as a tall challenge requiring multi-modal and multi-disciplinary approach. The Childrens Oncology Group trial for extra ocular retinoblastoma is likely to formulate an effective and standardized management protocol in the near future. Although the survival has increased over the last few years, lack of access to medical facilities, lack of education about the need for early medical attention and cultural resistance to enucleation continue to contribute to an epidemic of extra ocular disease at diagnosis in the developing world. The goals for the future needs to be well designed, implemented and spread over medical, socio-economic and research frontiers.

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LEGENDS FOR FIGURES

Figures 1a and 1b: Bilateral advance retinoblastoma. Left eye gross proptosis and right eye anterior segment seeding can be appreciated.(1a) CT Scan axial cuts of the same patient confirmed orbital mass and gross optic nerve extension.(1b)

Figure 2 : Primary orbital retinoblastoma. The right eye shows proptosis with extra scleral extension in the form of nodular masses.

Figure 3: Fungating orbital retinoblastoma.

Figure 4: Histopathology specimen of an enucleated eye demonstrating extra scleral extension of the tumor.

Figures 5a and 5b: CT Scan axial cuts shows gross left optic nerve thickening of the tumor measured radiologically.(4a) CT Scan axial cuts shows gross left optic nerve extension along with intracranial extension.(4b)

Figures 6a and 6b: Bilateral phthisical eyes following chemotherapy for advance retinoblastoma.(5a) CT Scans with saggital reconstruction of the same patient.(5b)

CLASS	FEATURE
Class I	Microscopic involvement of scleral emissaries
Class II	Microscopic involvement of cut end of optic nerve
Class III	Orbital disease in the biopsy
Class IV	CNS disease with brain mass or CSF with positive tumor cells
Class V	Blood borne metastasis to bone marrow, bone or lymphatic metastasis to lymph nodes

TABLE 1: Childrens Cancer Group Classification of Orbital Retinoblastoma

1. Primary Orbital Retinoblastoma
2. Secondary Orbital Retinoblastoma
3. Accidental Orbital Retinoblastoma
4. Overt Orbital Retinoblastoma
5. Microscopic Orbital Retinoblastoma

TABLE 2 : Clinicopathological Classification of Orbital Retinoblastoma

TABLE 3: SUGGESTED PROTOCOL FOR PRIMARY ORBITAL RETINOBLASTOMA

BASELINE INVESTIGATIONS

CT Scan or Magnetic resonance imaging
Bone marrow biopsy
Cerebrospinal fluid cytology

TREATMENT

Initial Chemotherapy ---- High dose triple-drug chemotherapy for 3-6 cycles every three weeks.

Surgery ---- Enucleation

1. Assessment of orbital tumor by imaging after completion of third cycle. If resolved than proceed with enucleation. If unresolved give additional 3 cycles of chemotherapy.

2. Assessment of orbital tumor after completion of 6 cycles. If resolved proceed with enucleation and if not proceed with exenteration.

Radiotherapy (External beam) ---- 45-50 Gy in fractionated doses to the orbit.

Subsequent chemotherapy --- Continuation of high-dose chemotherapy for 12 cycles.

FOLLOW-UP INVESTIGATIONS

Imaging at 12, 18, 24 and 36 months.
Bone marrow biopsy and cerebrospinal fluid cytology at 6, 12, 18, 24 and 36 months.

HIGH DOSE CHEMOTHERAPY (mg/kg body weight)

Vincristine --- Day 1 --- 0.025 mg/Kg

Etoposide --- Day 1 --- 12mg/kg
Day 2 --- 12mg/kg

Carboplatin --- Day 1 --- 28mg/kg

Figure 1a

Figure 1b

Figure 2

Figure 3

Figure 4

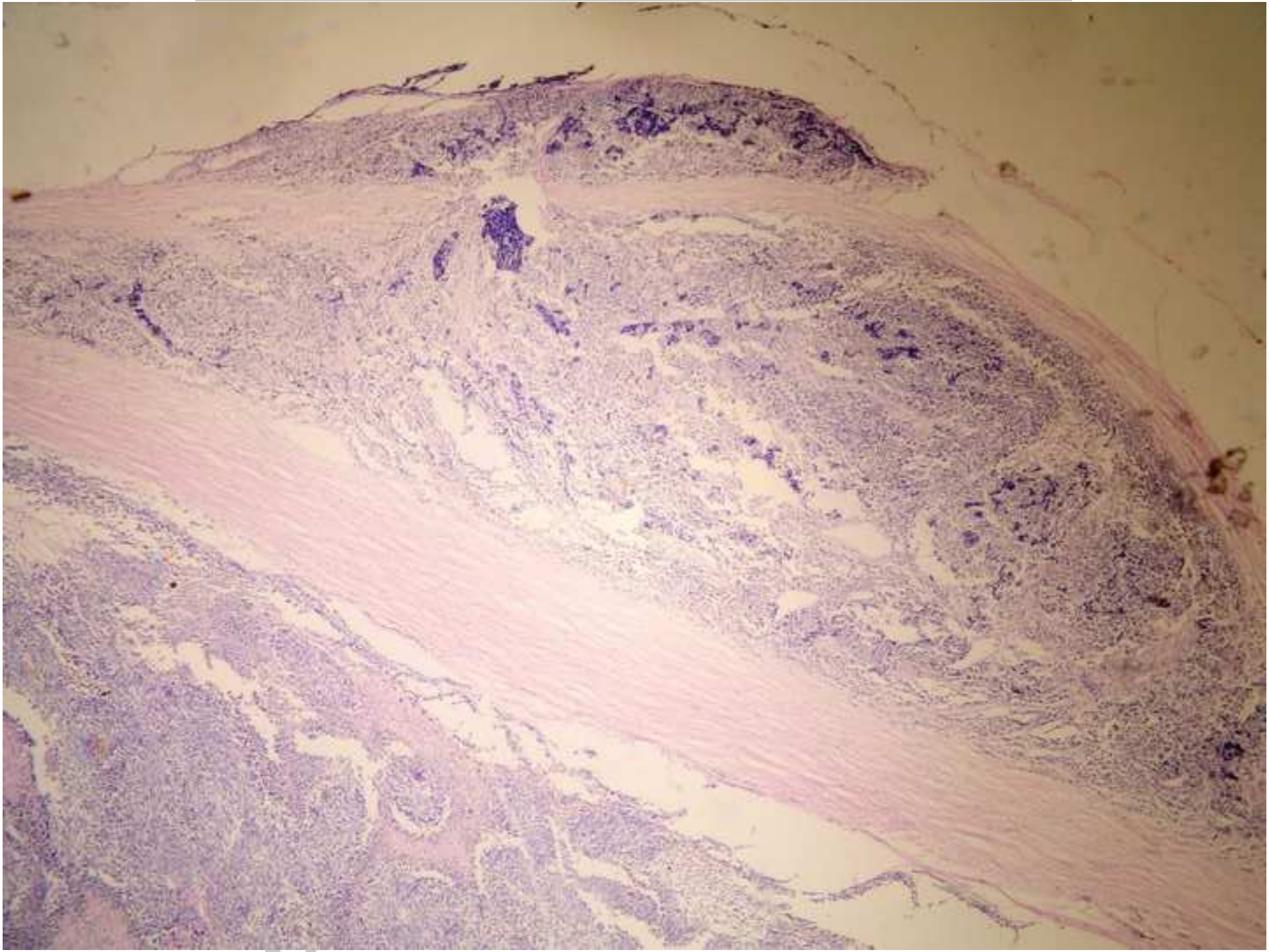

Figure 5a

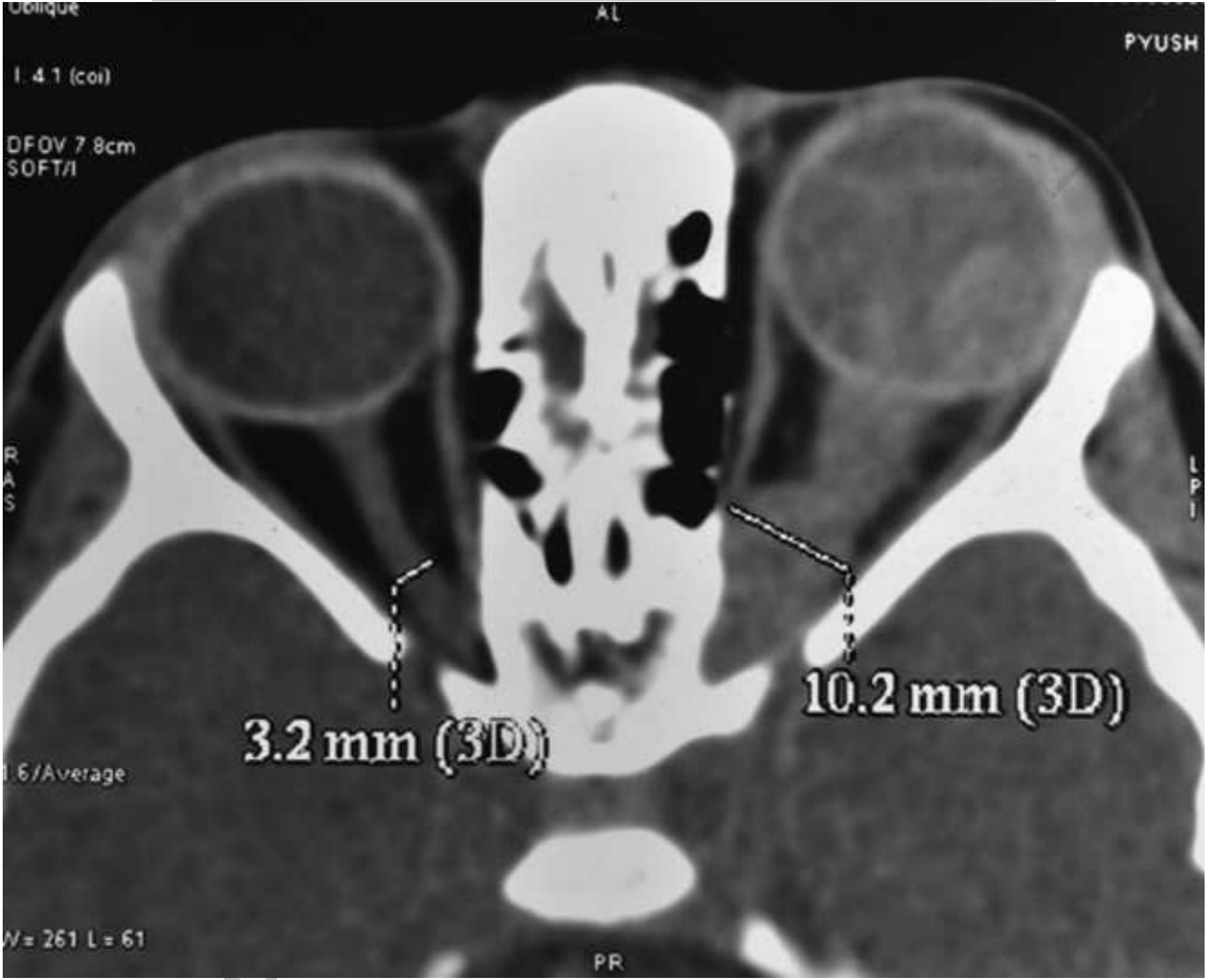

Figure 5b

Figure 6a

Figure 6b