Review Article

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Genetics and management of retinoblastoma

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ABSTRACT

Retinoblastoma is the most common intraocular tumor in childhood. In majority of early stage retinoblastoma, the eyeballs as well as vision can be preserved with chemotherapy and local intraocular therapy with laser or photocoagulation. However, more than half the patients in India and other developing nations present in advanced stage of the disease. This article reviews the genetics, clinical approach, and treatment options for retinoblastoma focussing on advances in chemotherapy for intraocular retinoblastoma (chemoreduction), as well as improvement in survival in advanced retinoblastoma with surgery, chemotherapy, radiotherapy, and bone marrow transplantation.

KEY WORDS: Childhood, genetics, retinal blastoma

Retinoblastoma originates from the retinal neuroepithelium that can differentiate into almost any type of outer or inner retinal cell, including photoreceptors. It is the most common intraocular tumor in childhood, occurring in 1 of 17000 to 24000 live births, independent of race and sex. Approximately, 80% of the cases occur before 4 years of age while 40% of cases occur during infancy. This article reviews the genetics, clinical approach, and treatment options for retinoblastoma focussing on advances in survival in extraocular retinoblastoma with chemotherapy and bone marrow transplantation.

GENETICS OF RETINOBLASTOMA

Retinoblastoma may occur as nonhereditary or hereditary tumor. Tumors in nonhereditary retinoblastoma (60% cases) are typically solitary and unilateral with no family history and no detectable chromosomal abnormalities. Although <10% of cases of retinoblastoma have a positive family history, about 40% of retinoblastoma are of hereditary origin caused by a germline mutation in RB1 gene on chromosome 13q14. This is due to the majority being the result of a *de novo* mutation in the RB1 gene. Amongst those with hereditary retinoblastoma (40% cases), 25% cases have bilateral disease while 15% have unilateral disease. Hereditary RB1 mutations are found in all cells thereby increasing risk of other cancers, in particular, osteosarcoma and malignant melanoma.

Inherited retinoblastoma is transmitted as an autosomal dominant trait with high but incomplete penetrance. Children of patients with hereditary retinoblastoma have a one in two chance of carrying the germ cell mutation and for those who are carriers, the probability of developing retinoblastoma is very close to 90% if parents have bilateral retinoblastoma but probably less if they have the unilateral form.[1]

The probability of developing retinoblastoma in offsprings and siblings of patients is higher than in the general population because of which they need genetic counseling [Table 1] so as to effectively counsel and diagnose retinoblastoma early in high risk subjects. In bilateral cases or those with a positive family

Table 1: Risk of developing retinoblastoma in siblings and off springs of patients

Subjects	Probability of disease %
Subjects with carriers of RB1 gene mutation	90
Offspring of patient	45
Sibling of patient (if either parent is affected)	45
Sibling of patient with bilateral disease	2
Sibling of patient with unilateral disease	1

history, one can directly perform the genetic studies on peripheral blood sample as they would always be due to germline mutation in RB1 gene. In unilateral cases and those with a negative family history, there is only 15%-20% chance that somatic cells would also carry the mutation. Therefore, in these cases, genetic studies for RB1 gene mutation are initially performed in the tumor specimen, and subsequently, once the mutation has been identified, peripheral blood is screened to determine if it is a germline mutation (hereditary retinoblastoma) or non hereditary retinoblastoma [Figure 1].

If genetic testing is not pursued, then tumor surveillance for all siblings of the affected patient is recommended, which includes examination under anesthesia (EUA) at birth and every four months until the age of 4 years. On the contrary, if genetic testing demonstrates that the sibling did not inherit RB1 gene mutation, the surveillance and anesthesia required for eye examinations can be avoided, thereby decreasing costs and potential morbidity. Further, in unilateral retinoblastoma, if it can be demonstrated that the child does not carry a germline RB1 gene mutation, then (a) the child is not at substantial risk for second malignancies; (b) radiation therapy is associated with less hazards and; (c) the parents and eventually the child have a negligible risk of having another child with retinoblastoma.

CLINICAL PRESENTATION

The median age of diagnosis is 2 years. Bilateral retinoblastoma occurs earlier than unilateral disease. Majority of retinoblastoma in developed nations presents as an intraocular disease wherein 90% of cases are curable. However, in the developing nations, still 65% of patients may present with extraocular disease. An unpublished data from our center showed that mean age of presentation of unilateral retinoblastoma is 34 months, while that of bilateral disease is 24 months, which is higher than that in the west. The mean duration of symptoms was 8 months prior to visiting the tertiary care center, and 49% of patients presented with extraocular disease. This may be due to the lack of awareness, delayed referrals, and/or more aggressive disease biology. From a therapeutic point of view, retinoblastoma presentation may be divided into the following subtypes:

A. Early stage intraocular disease (preservation of eye possible) presents most commonly with leucocoria (white reflex with an ophthalmoscope) followed by strabismus. Therefore, a pediatrician should always include the documentation of a red reflex with an ophthalmoscope in examination of newborn and at subsequent well baby visits of a child. The absence of red reflex or strabismus merits an examination by an ophthalmologist in order to detect early stage intraocular retinoblastoma.
B. Advanced intraocular retinoblastoma (needs enucleation) presents with rubeosis iridis, hyphema, hypopyon, and glaucoma. The potential diagnosis of retinoblastoma should always be investigated in a child presenting with spontaneous hyphema in the absence of trauma or who presents with signs of endophthalmitis. Pain is not a feature of intaocular retinoblastoma unless secondary glaucoma or inflammation is present.
C. Extraocular retinoblastoma presents with proptosis, preauricular lymphadenopathy, bone pain, features suggestive of bone marrow or central nervous system involvement.

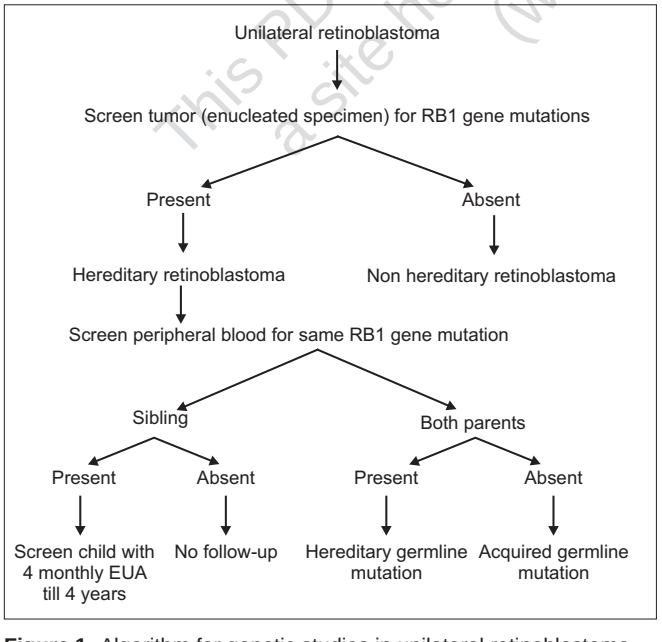

Figure 1: Algorithm for genetic studies in unilateral retinoblastoma

Investigations

The diagnostic work up includes EUA of the eye and ultrasonography and CT scan of the orbit and head to confirm the diagnosis of retinoblastoma, and to detect ectopic disease in the pineal gland. The clinical presentation and ancillary radiological findings are typical for retinoblastoma in majority of the patients, and a tissue biopsy is not required for confirmation prior to the therapy. However, a fine needle aspiration biopsy may be performed in select cases of pediatric ophthalmological disease where the diagnosis is in question. Metastatic work up includes cerebrospinal fluid examination for malignant cells and bone marrow biopsy and bone scan in those with extraocular disease. Intraocular retinoblastoma is traditionally classified by Reese-Ellsworth (RE)[2] classification [Table 2], whereas intraocular and extraocular retinoblastoma is classified according to Grabowski-Abramson[3] staging [Table 3].

MODES OF THERAPY IN RETINOBLASTOMA

The aim of treatment in retinoblastoma is to cure the patient with preservation of vision; the second aim is to minimize the long-term effects of therapy. With advances in therapy, the survival has risen from 30% in 1930's to nearly 95% in 1990's for non-metastatic retinoblastoma. However, untreated retinoblastoma is always fatal. The major therapies that have resulted in this improved survival are enucleation and external beam radiation therapy (EBRT), both of which are associated with significant morbidity.

A. Enucleation cures localized retinoblastoma but at the cost of loss of sight. Apart from its obvious adverse physiologic and psychological effects, enucleation can be associated with chronic local effects such as discharge from orbit, contraction of socket, and extrusion of implant. Thus, there is a need for relatively non-invasive focal ophthalmological therapies.
B. EBRT provides good local control in retinoblastoma when used in conjunction with local non-invasive ophthalmological therapies. However, it has significant local side effects such as xerophthalmia, cataract, retinopathy, and keratopathy; it often does not spare vision. It adversely affects midface growth in 90% of the patients. The risk of secondary non-ocular malignant tumors increases 6-fold after EBRT especially in those with germline mutation of RB1.[4-6] Patients carrying RB1 germline mutation have a 35% cumulative risk of secondary cancers in the radiation field by the age of 30 years, whereas those who do not have RB1 mutation have a risk of 6%. This effect may be age dependent with the greatest risk in those retinoblastoma patients with hereditary disease treated under-1 year of age. The cumulative risk of death from secondary tumors is 26% at 40 years of age. Plaque radiotherapy avoids long-term complications of EBRT, but this cannot be used in large tumors, tumors with vitreous seeding, or tumors at posterior pole.
C. Chemotherapy is one of the possible treatment modalities, which is free from long-term effects of radiation. Drugs commonly used in retinoblastoma include vincristine, adriamycin, idarubicin, cyclophosphamide, cisplatin, carboplatin, and etoposide. Carboplatin is preferred over cisplatin because of its reduced ototoxicity and nephrotoxicity profile as compared to cisplatin. An increased incidence of secondary primary tumors has been attributed to the use of cyclophosphamide and etoposide in children with RB1 mutations. Recently, combination of vincristine, etoposide, and carboplatin (VEC) is the preferred drug combination [Table 4]. Carboplatin has good penetration in eye, brain, and bone marrow, which are two potential sites for metastatic disease in retinoblastoma. Multidrug resistance is caused by overexpression of membrane-associated energy-dependent drug efflux pump, the P-glycoprotein. The P-glycoprotein is encoded by *mdr1* gene and cells with multidrug resistance often show amplification of this gene. Although, the effect of P-glycoprotein is reversible

Table 2: Reese-Ellsworth classification of retinoblastoma

Group I - Very favorable prognosis
A. Solitary tumor, less than 4 disc diameters (dd)* in size, at or behind the equator
B. Multiple tumors, less than 4 dd in size, all at or behind the equator
Group II - Favorable prognosis
A. Solitary lesion 4-10 dd in size, at or behind the equator
B. Multiple tumors, 4-10 dd in size, behind the equator
Group III- Doubtful prognosis
A. Any lesion anterior to the equator
B. Solitary tumors larger than 10 dd behind the equator
Group IV - Unfavorable prognosis
A. Multiple tumors, some larger than 10 dd
B. Any lesion extending anteriorly to the ora serrata
Group V - Very unfavorable prognosis
A. Massive tumors involving over half the retina
B. Vitreous seeding

*One disc diameter = 1.6 mm

Table 3: Grabowski and Abramson staging for intra- and extra-ocular retinoblastoma

Intraocular disease
a. Retinal disease
b. Extension to lamina cribrosa
c. Uveal extension
Orbital disease
a. Orbital tumor
1. Scattered episcleral cells
2. Orbital invasion
b. Optic nerve
1. Invasion upto cut end
2. Invasion beyond the cut end
Intracranial metastasis
a. Positive cerebrospinal fluid alone
b. Mass lesion in the central nervous system
Hematogenous metastasis
a. Positive bone marrow alone
b. Focal bone lesions with/without bone marrow disease

Table 4: Chemotherapy vincristine, etoposide, and carboplatin protocol

A. Drugs
Vincristine 1.5 mg/m^2 day 1 (0.05 mg/kg for children <3 years and max dose 2 mg)
Carboplatin 560 mg/m^2 day 1 (18.6 mg/kg for children <3 years)
Etoposide 150 mg/m^2 days 1 and 2 (5 mg/kg for children <3 years)
B. Cycles
Every 3-4 weeks;
Ensure ANC >1000 and platelets >100,000/mm^3
C. Number of Cycles
2-6 cycles for chemoreduction
6 cycles for chemoprevention
6-12 cycles for systemic disease

with high concentrations of cyclosporine and might even be diminished in future by using MoAbs against P-glycoprotein, role of cyclosporine in reversing drug resistance in patients with retinoblastoma remains unclear in absence of a randomized trial.[7]

Chemotherapy is used in retinoblastoma in three settings: intraocular RB, micrometastatic RB, and overt dissemination.

CHEMOTHERAPY IN INTRAOCULAR RETINOBLASTOMA (CHEMOREDUCTION)

Chemoreduction is the use of chemotherapy to shrink the tumor so that local treatment can be delivered to a smaller volume and cause less morbidity. This technique has been employed in an effort to avoid or at least delay EBRT and enucleation for children with retinoblastoma, especially those with bilateral disease. The great advantage of chemoreduction in retinoblastoma seems to be the ability to move the tumor margins away from visually vital structures, such as optic disc and foveola.

Retinal tumors generally respond rapidly to chemoreduction; residual tumors can thereafter be destroyed without vision loss by using adjuvant local brachytherapy, photocoagulation, cryocoagulation, and/or laser therapy. Eyes with additional vitreous seeds or subretinal seeds are managed differently using chemoreduction without focal consolidation treatments because the number of seeds is usually far beyond the capability of focal treatment methods and the multitude of tiny seeds typically respond with regression, calcification, and often complete disappearance after several months of treatment. In applying this strategy in the management of bilateral retinoblastoma, it seems appropriate to conserve both eyes at first. The decision to enucleate one eye can be postponed at least until early response to primary chemotherapy has been assessed. It is then easier to judge which eye is salvageable and which not.

Chemotherapy is administered every 3-4 weekly for 2-6 cycles. Patient requires tedious monitoring every 2-3 weekly by examination under anesthesia of the affected eye. Chemotherapy by itself is not sufficient to cure retinoblastoma, and so, additional focal treatment is mandatory since histopathological evaluation still reveals viable proliferating tumor cells after 2-6 cycles.[8] At any suggestion of tumor progression, the eye needs enucleation or EBRT. A regimen with fewer than 6 cycles is less effective in preventing enucleation or EBRT, especially in eyes with Reese-Ellsworth (RE) stages IV and V.[9]

Efficacy of chemoreduction

An early volume reduction of around 50% after two courses of VEC can usually be expected.[10] The overall salvage of eyes in the chemoreduction studies is about 80%. EBRT was added in an additional 30% of the salvaged eyes. Thus, approximately 50-60% of affected eyes treated with chemoreduction are successfully preserved with avoidance of EBRT or enucleation.[11] The rate of globe preservation is best with less advanced eyes (85%), such as those in RE groups I to IV whereas with more advanced eyes, such as those in RE group V, preservation is less successful at <50%.

In a study by Shields *et al*.,[12] chemoreduction using six cycles of VEC offers satisfactory retinoblastoma control for RE groups I-IV eyes, with treatment failure necessitating additional EBRT in only 10% of eyes and enucleation in 15% of eyes at 5-year follow-up. Patients with RE group V eyes required EBRT in 47% and enucleation in 53% at 5 years. Thus, all localized intraocular retinoblastoma have a potential for eye preservation using chemoreduction [Figure 2]. However, any evidence for potential micrometastatic disease or overt metastatic disease should be excluded from chemoreduction [Table 5].

Recurrence of retinoblastoma following chemoreduction

The mean interval from discontinuation of chemoreduction to first recurrence of retinal tumor was 4

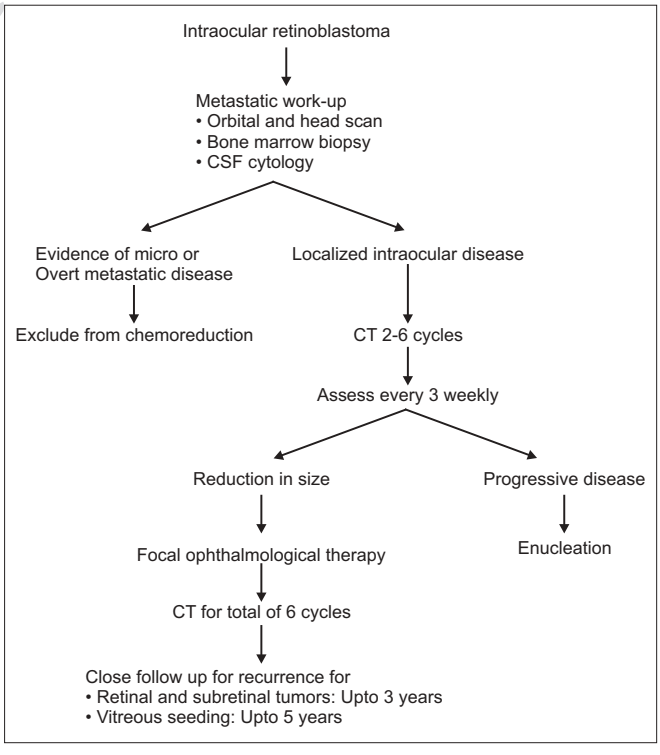

Figure 2: Algorithm for management of intraocular retinoblastoma

Table 5: Exclusion criteria for treatment with chemoreduction

- Biomicroscopic evidence of iris neovascularization
- Neovascular glaucoma
- Tumor invasion into the anterior chamber, iris, optic nerve and/or choroid
- Extraocular disease as documented by clinical, ultrasonographic, and neuroimaging modalities
- If vitrectomy is performed for an eye with unsuspected retinoblastoma

months, recurrence of vitreous seeds was 2 months, and recurrence of subretinal seeds was 2 months.[13] Thus, monitoring of the eye is especially critical following chemoreduction to detect recurrence. It is reassuring to know that most children manifest their recurrent retinal tumors and subretinal seeds by 3 years after treatment with little recurrence thereafter; accordingly, follow-up can be adjusted for this time interval. Vitreous seed recurrence, however, continues to be a problem up to 5 years after treatment and potentially longer; therefore, patients with vitreous seeds at initial examination might require cautious ocular examination for many years following treatment.

At 5-year follow-up, the recurrence rates for intraretinal tumors, vitreous seeds, and subretinal seeds were seen in 24%, 50%, and 62% of eyes, respectively.[13] Those at greatest risk for retinal tumor recurrence are eyes with tumor-associated subretinal seeds surrounding the base of the tumor. Patients at greatest risk for vitreous or subretinal seed recurrence are those who, at initial examination are younger, had large tumor dimensions, and had tumor-associated subretinal seeds. All children receiving a chemoreduction protocol should be monitored by retinoblastoma specialist who is able to detect minute recurrences and capable of treating the recurrences.

CHEMOTHERAPY FOR RETINOBLASTOMA POST-ENUCLEATION (CHEMOPREVENTION)

With improved understanding of risk factors predictive of metastasis and availability of effective chemotherapy regimens for intraocular retinoblastoma, it would seem logical to consider chemotherapy following enucleation to prevent metastasis in high-risk cases; this is referred to as chemoprevention. Various histopathological factors have been identified as potential risk factors for retinoblastoma [Table 6]; however, there is some controversy as to whether choroidal involvement alone is a significant risk factor for metastases.[14-16] The current strategy is to give 6 cycles VEC to prevent metastases, and the rate of metastasis is significantly reduced in the group receiving chemoprevention as compared with the group that did not receive chemotherapy (4% vs. 24%).

Table 6: Post-enucleation specimen (histopathological criteria for chemoprevention)

Indications for chemoprevention
Anterior chamber seeding
Iris infiltration
Ciliary body infiltration
Massive choroidal infiltration
Invasion of optic nerve lamina cribrosa
Retrolaminar optic nerve invasion
Invasion of optic nerve transection*
Scleral extension*
Indications for no additional chemotherapy
Intraretinal extension
Prelaminar optic nerve invasion

*These require additional EBRT as this is considered as extraocular disease limited to orbit

Kaplan-Meier estimates showed that 96% of patients who received adjuvant therapy would remain free of metastasis at 10 years post-enucleation compared with 76% of those who did not receive adjuvant therapy.[15]

Chemoprevention following vitrectomy

Retinoblastoma may present with atypical features such as vitreous hemorrhage or signs of vitreous inflammation, particularly in older children. Vitrectomy should be avoided in these cases until the possibility of underlying retinoblastoma is excluded. If vitrectomy is performed in an eye with unsuspected retinoblastoma, enucleation combined with chemotherapy, radiotherapy or both without delay is advised to prevent systemic tumor dissemination.[17]

Chemotherapy for extraocular retinoblastoma

Metastatic retinoblastoma is seen in less than 10% cases in developed nations whereas almost two-third of cases of retinoblastoma in developing countries. Chemotherapy is indicated in all these situations and is used in the following two fashions:

1. Conventional chemotherapy wherein the same drugs are used as is used in chemoreduction or chemoprevention, but for a longer duration of 6-12 months.
2. High dose chemotherapy (HDT) wherein after initial conventional chemotherapy, the patient is consolidated with high doses of the same agents and bone marrow rescued with an autologous stem cell transplantation (ASCT).

Two different subgroups of patients with extraocular retinoblastoma with different outcome can be distinguished [Figure 3] as follows:

A. Extraocular disease limited to orbit alone (invasion upto or beyond the cut end of optic nerve; scleral invasion upto the orbital contents) or with concomitant lymph node invasion. These patients have a 5-year progression free survival of >80% using initial exenteration followed by intensive chemotherapy

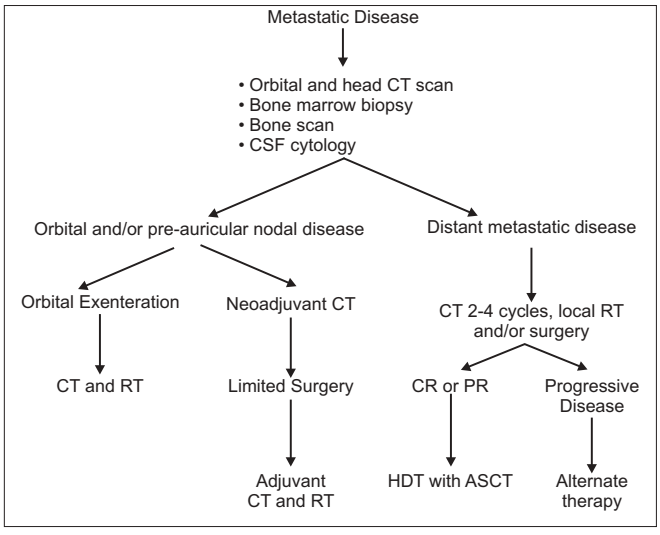

Figure 3: Algorithm for management of metastatic retinoblastoma

and radiotherapy.[18] Similar results have also been obtained using initial neoadjuvant chemotherapy followed by limited surgery (enucleation or resection of residual orbital mass) and adjuvant therapy and radiotherapy.[19] Comparable results have been reported using HDT with ASCT. Thus, HDT in these two situations seems to be a therapeutic alternative with the advantage of shorter duration of therapy.[20] Further, most of the failures or recurrences are in the CNS, and thus, intrathecal chemotherapy is used by some centers along with chemotherapy.

B. Those with systemic and/or CNS dissemination (bones, bone marrow, positive CSF cytology, or mass lesion in brain) are seldom cured with conventional chemotherapy. However, HDT using carboplatin, etoposide, and cyclophosphamide is effective in patients with chemosensitive retinoblastoma patients with distant metastatic disease, except those with CNS disease.[21] Prognosis is extremely poor in those with CNS disease. CNS irradiation, as is currently employed, does not cure CNS disease. Role of intrathecal therapy using methotrexate, cytosine arabinoside, and hydrocortisone, as is employed in CNS leukemia, is debatable. Thus, more effective therapeutic strategies are required to cure CNS disease in retinoblastoma.

CONCLUSION

Retinoblastoma is a chemosensitive disease but cannot be cured with chemotherapy alone. It is a very effective mode of therapy in preserving vision and the long-term complications of enucleation and EBRT, especially in intraocular retinoblastoma. Metastatic retinoblastoma to the orbit can be treated with good results with combination chemotherapy, radiotherapy, and possibly, conservative eye surgery as well. Distant metastatic disease cannot be cured with conventional chemotherapy in majority of the cases; however, HDT with ASCT appears to be a promising therapy for such cases. Retinoblastoma with CNS metastases continues to have dismal prognosis despite HDT with SCT and/or cranial radiation.

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