RETINOBLASTOMA FAMILIAL IN A 3-YEAR-OLD GIRL

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ABSTRACT

Retinoblastoma is the commonest intraocular tumor in childhood. About one thirds of all cases are bilateral. It is recognized that bilateral and familial retinoblastoma are cause by germline mutation and are thus a heritable tumor. We reported a case, 3-year-old girl showing proptosis of the right eye since six months before admission. She had family history (his father) of retinoblastoma. Physical examination showed mass of the righ eye and leucorea of the left eye. Computed tomography scan showed retinoblastoma extraoccular of the right eye and retinoblastoma intraoccular of the left eye without spread to the pinealis gland or Parsellar**.** Bone marrow aspration showed non hemopoitic cell (metastatic tumor). Patient was diagnosed with bilateral retinoblastoma familial grade V. Despite the management of this patient is chemotherapy and still on treatment chemotherapy continuous phase, the prognosis still worse. **[MEDICINA 2013;44:128-134]**

Keywords: *retinoblastoma, bilateral, familial, bone marrow, metastasis*

FAMILIA RETINOBLASTOMA PADA ANAK PEREMPUAN 3 TAHUN

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ABSTRAK

Retinoblastoma merupakan tumor intraokuler yang paling sering terjadi pada anak. Sepertiga kasus merupakan bilateral retinoblastoma. Penyebab retinoblastoma bilateral dan familial adalah mutasi germline dan tumor yang diturunkan. Kami melaporkan kasus, perempuan, usia 3 tahun dengan keluhan mata kanan menonjol sejak 6 bulan sebelum masuk rumah sakit. Ada riwayat retinoblastoma pada ayah pasien. Pemeriksaan fisik didapatkan massa pada mata kanan dan leukorea pada mata kiri. *Computed tomography scan* menunjukkan retinoblastoma ekstraokuler pada mata kanan dan retinoblastoma intraokuler pada mata kiri tanpa penyebaran ke kelenjar pinealis atau parsaellar. Aspirasi sumsum tulang menunjukkan sel non-hemopoitik (tumor metastase). Pasien didiagnosis retinoblastoma bilateral familial stadium V. Meskipun tata laksana kemoterapi pada pasien masih berlanjut, namun prognosisnya buruk. **[MEDICINA 2013;44:128-134]**

Kata kunci: retinoblastoma, bilateral, familial, bone marrow, metastasis

INTRODUCTION

Retinoblastoma is the most common intraocular malignancy found in children.[1-3] It represents approximatelly 4% of all pediatric malignancies. It is estimated that 250 to 300 new cases of retinoblastoma are diagnosed in the United States each year, 5000 cases are diagnosed worlwide and about 1 child in 15.000–18.000 live birth in the developed country, esspecially in the Afrika and Asia.[1,3] Untreated, retinoblastoma is almost uniformly fatal, but with availability of resources for early detection and treatment, the survival rate has improved from aproximately 30% in the 1930 to over 90% in the 1990s in developed countries. However, in the developing countries, the majority of patients with retinoblastoma present with advanced disease with resultant 5 year survival of less than 50%.[4-6]

Accurate diagnosis in child with suspected retinoblastoma is accomplished by taking a detailed history, physical evaluation, external occular examination, slit lamp biomicroscopy and binocular indirect opthalmoscopy with scleral indentation. Needle biopsy confirmation is rarely.

Ultrasound and CT scan can demonstrate intraocular tumor.

Magnetic resonas imaging (MRI) can use to do the assessment of the optic nerve, orbit, and brain.[3,5]

The most important objective in the management of a child with retinoblastoma is survival of the patiens. Therapy is tailored to each individual case and based on the overall situation, including threat of metastatic disease, risk for second cancer, systemic status, laterality of the disease, size and location of the tumor and estimated visual prognosis. The curently available treatment methods for retinoblastoma include intravenous chemoreduction, thermotherapy, cryotherapy, laser photocoagulant, plague radiotherapy, external beam radiotherapy, enucleation, orbital exentration and systemic chemotherapy for metastatic disease.[3,5]

The monitoring of patients with retinoblastoma and their family is crucial. Earlier detection of the tumor influence the prognosis and in recent years has allowed for more conservation eye sparing treatment of retinoblastoma.[3,5]

Familial inheritance of retinoblastoma care is very rare, only 6 % of newly diagnosed retinoblastoma cases are familial. We reported a 3 years oldgirl with familial retinoblastoma grade V.

CASE REPORT

KNA, a 3-year-old girl was admited to the Pediatric Departmen Sanglah Hospital at February 12th 2011, referred from Opthalmologist Departement of Sanglah Hospital with retinoblastoma pro chemotherapy, with chief complaint mass of the right eye or protruding right eyes (proptosis) **(Figure 1).** Proptosis was occured since six months before admission, became larger, painfull, and redness. There was history of strabismus of the right eye 1 years before admission and there were no complaint about cat's eye or shiny white spot vitreous hemorrhage, hypema, occular or periocular inflamation, glaucoma, proptosis, and hypopion, then the patient was brought to the opthalmologist, got medication vitamin, and advised to do focus excercise at home. Since eight month before admission her parents also complained cat's eye or shiny white spot of the right eye **(Figure 2**), and poor vision then they brought to the Opthalmology Department of Sanglah Hospital, diagnosed with suspected retinoblastoma and planned CT scan, but the parents refused. Shiny white spot of left eye was complained since four months before admission and no vision were acquired. There were no complaint about painfull eyes or red eyes of the left eye. There was no history of trauma.

She was born spontaneously, fully termed and was assisted by a local midwife. Her birth weight was 2900 gram and birth body length was 50 cm. No visible abnormality was found. She did not get any prior medication for spesific disease. Her father had a history of retinoblastoma on right eye and had been enucleated when he was 3 years old. The immunization history was completed according to the recommended imunization plan by the government. According to the nutritional history, the patient was given breast milk until 2 years old and got formula milk since 1 years old until now. Steamed cook rice was given at 7 to 12 months old. Adult food was given at 1 years old until now. Types of food that she usually takes are rice, vegetable, meat and egg. Her growth and development was within normal limit until three years old. She could roll over at 4 months old, sit at 8 months old and crawl at 10 months old. At 14 months old, she could walk unassistedly. She could say the word " bapak " and "memek" at 14 months old, and at this point of time she could say many words clearly. Since 6 month before admission, daily activities were limited, she couldn't do well in social activities. Family history was her father's history of retinoblastoma on the right eye with the clinical manifestation were strabismus and cat's eye or shiny white spot. There were no complaint about vitreous hemorrhage, hypema, occular or periocular inflamation, glaucoma, proptosis and hypopion and had been operated (enucleasi) when he was three years old.

Physical examinations revealed good consciousness, arterial pulse was 100 times per minute, respiration rate was 28 time per minutes, axillary temperature was 36,8^0 C, blood pressure was 110/70 mmHg. Her body weight was 10 kg (the <5th percentile, CDC 2000), body height was 90 cm (at the <5th, CDC 2000), upper arm circumference was 19 cm, head circumference was 49 cm (within ±2 SD). Her ideal body weight was 13 kg. Thus according to the Waterlow criteria, her

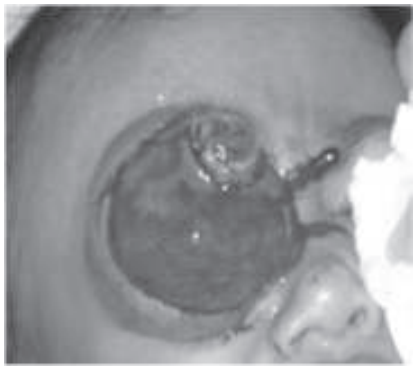

Figure 1. Mass of the right eye.

Figure 2. Leucorea of the left eye.

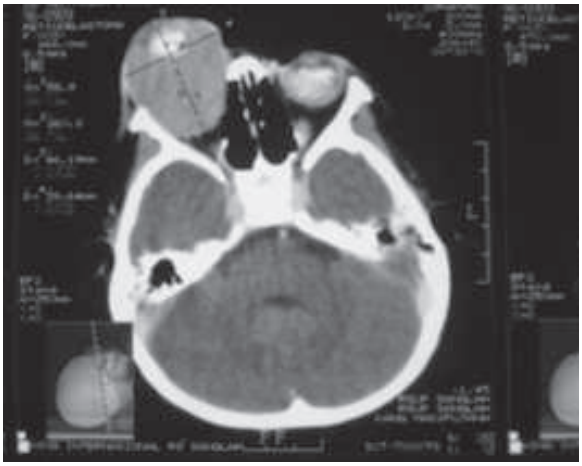

Figure 3. Axial CT image showing

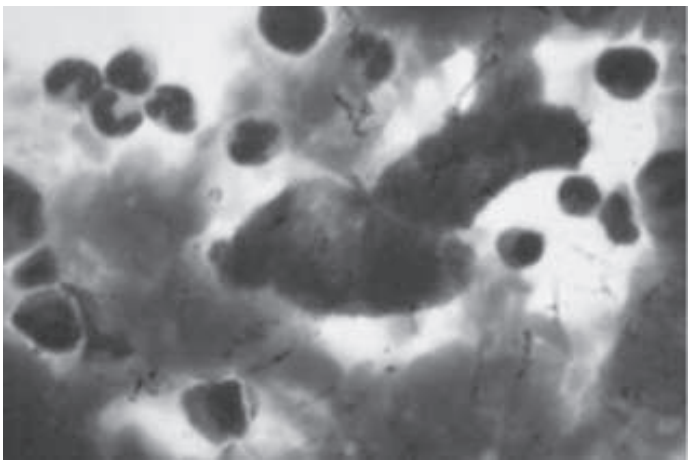

Figure 4. Bone marrow aspiration showed retinoblastoma non hemopoietic cell (metastatic tumor).

nutritional status was mild malnutrition (76,96%).

Her hair was fine and black. The right eye examination showed visual acuity had no light perception, edema palpebra. Mass of the right eye, size mass was 5x4x2 cm, soliter, smooth surface, solid, fragile, fixated. Camera occuli of the right eye couldnot be evaluated because the cornea was hazy and mealting. The left eye examination showed visual acuity had no light perception and palpebra was normal, conjungtiva hiperemis, sclera was not jaundice, clear cornea, camera occuli anterior was normal. Posterior segment examination with direct opthalmoscope by opthalmologist showed leucorea and pundus reflexes were negative.

The ear nose and throat as well as neck examination were within normal limit. There was no any palpable lymph nodes or nuchal rigidity. The chest examination revealed no precordial bulging. Ictus cordis was palpable on the 5th intercostals space on the left midclavicular line. There were no thrill and no RV heave. On auscultation, the first and second heart sounds were normal, without murmur. The movement of both sides of the chest was symmetrical. Vesicular respiratory sounds were noted, without wheezing or rales. The abdomen examination revealed no hepatomegaly and no splenomegaly. There was no baggy pants. The examination of upper and lower extremities showed no deformity. There was no edema, no cyanosis and the capillary refill time was normal. The physiological reflexes of the patella and achilles tendon were normal. Motor strength in the extremities were normal and no pain of the bone.

Based on anamnesis and physical examination, working diagnosis for the case was mass on right ocular dextra et causa suspected retinoblastoma, differential diagnosis were rabdomiosarkoma orbital and selulitis orbita. We planned for further examination such as orbita computed tomography scaning, complete blood count, cells blood smear, reticulosite, lumbal punction, bone marrow aspiration, genetic testing using DNA analysis.

The laboratory investigation showed a complete blood count of WBC 6.96 k/µL (neuthrophil 62.8%; lymphocyte 23.7 %; monocyte 8.6%; eosinophil 0.7%; basophil 0.7 %); Hb 12.4 g/dl; MCV 78.3 fL; MCH 22.3 g/dL; MCHC 31.1 g/dL; RDW 14.9%; Hct 39.9%; RBC 5.5 g/dL and platelet 352 k/µL, reticulocyte 0.8. .LDH 819 IU/L. Blood smear examination revealed erytrosit: normocromic, normositer; leukocyte count : normal limit with normal differentiated count; thrombocyte: normal limit; conclusion: normal.

Orbita and head axial enhancement CT with and without contrast demonstrated the solitary mass with calcification in the right bulbus ocullar which spread in to the right cavum orbita. Size mass was 4,6 x3.9 x 3.6 cm and infiltration righ musculus extraocculer (m. rectus lateralis dextra and m. rectus medialis dextra) and right nervus opticus distal, with the destruction of the right maxillary superior sinus wall. Computed tomography scan also demonstrated the solitary mass with calcification in the left bulbus ocullar. With no spread into the right cavum orbita. Left musculus extraoccular and nervus opticus were normal. Computed tomography scan did not showed infiltration in the paranasalis sinus. Intracranial structure was normal and not showed mass in glandula pinealis. Conclusion : right and left retinoblastoma, which spread into the extraconal right orbita, with intracranial structure normal **(Figure 3).**

Bone marrow aspiration (BMA) showed cellularity : normocellular, erytroid/myeloid/megakariosit cellularity were normal activity with non hemopoetic cell. Conclusion : showed non hemopoitic cell (metastatic tumor) **(Figure 4).**

Liquor cerebrospinal showed mature lymphocyte cell <10 cells, not showed the other nucleated cell. Chromosome analysis from blood with G-banding technique was studied 20 cells chromosome showed major structure was normal. Based on the anamnesis, clinical manifestation, and laboratory findings, the patiens was diagnosed with retinolastoma.

Management of these patient was primary systemic chemotherapy (chemoreduction) with protocol extraocular retinoblastoma 2002. Chemoreduction for retinoblastoma have employed cyclophospamide, doxorubicin, vincristin, cytocin arabinase, methotrexate intratecal. Total cycles for chemoreduction need 105 weeks, for intensive phase chemotherapy was given every week and continuous phase every three week. After finished chemotherapy intensive phase, proptosis of the right eye was smaller than before the chemotherapy**.** The patient is still on treatment chemotherapy continuous phase.

DISCUSSION

Retinoblastoma represents approximately 4% of all pediatric malignancies and is the most common primary intraocular cancer in children. It represents approximatelly 4% of all pediatric malignancies. Retinoblastoma is typically diagnosed during the first year of life in familial and bilateral case and betwen age 1 years old and 3 years old in sporadic unilateral case. Onset later than age 5 years old is rare but can occur. Retinoblastoma is an endooccular tumor of the neuroembrionic retina (neuroblastic tumor) in children. Biologically similar to neuroblastoma and meduloblastoma. It caused by genetic defect in the retina.[1,5-7]

The most common initial sign is leucorea (white pupil), which is noticed by the family and described as glow, glint or cat's-eye appearance. Strabismus is the second major presenting sign of retinoblastoma. Less common presentations include vitreous hemorrhage, hypema, occular or periocular inflamation, glaucoma, proptosis and hypopion. The clinical presentation of retinoblastoma is depend on tumor growth pattern (intrarenal, endophytic and exophytic), duration of growth, degree of tumor vascularity, the presence or absence of calcifications, vitreus seeding and retinal detachment.[1,3,5] **In our case, a 3 year old girl with protruding right eyes (proptosis) and shiny white spot or cat's eyes on the left eye. There was history of strabismus on the right eye 1 year before admission, painfull and red eyes, poor vission, and occular inflamation.**

Accurate diagnosis in a child with suspected retinoblastoma is accomplished by taking a detailed history, physical evaluation, external ocular examination, slit lamp biomicroscopy, and binoccular indirect ophthalmoscopy with scleral indentation. This is generally performed with or without local anesthesia in order to determine precisely the number and location of all tumors. The diagnosis is established by the classic appearance of the retinal tumors by an experienced examiner. Retinoblastoma is one of rare child cancer which can accuratelly diagnosed without histopathology confirmation. Needle biopsy confirmation is rarely, if ever, necessarily because such procedures can disseminate malignance cells. Fluorescein angiography shows early vascularity and late hyperfluorescence of the tumor. Ultrasonography and computed tomography can demonstrate the intraocular tumor and possibly detect calcium within the mass. Approximately 5% to 10% of retinoblastomas show no intrinsic calcification. Magnetic resonance imaging does not usually detect calcium but may be valueble in the assessment of the optic nerve, orbit, and brain. Optic coherence tomography has been found useful in the detection of cystic retinoblastoma that might show less dramatic response to chemotherapy, and it is also helpful in the follow-up of patients to assess macular anatomy. There were intraoccular calcification from USG, CT or MRI imaging showed suspected retinoblastoma but no patognomonic. Aspiration and biopsy of bone marrow and lumbal punction for sitology test can be done if showed extraocculer spread. Lactate dehidrogenase (LDH) serum or needle biopsy can differensiate retinoblastoma with the other lession which can produce LDH.[3,5,7,8]**. In our case, from physical evaluation, external ocular examination, and binocular indirect ophthalmoscopy under anesthesia by an experienced examiner opthalmologist, showed visus with no light perception, proptosis of the right eye and left eye was normal, conjungtiva hiperemis of the right and left eyes, cornea is clear on the right and left eyes, camera occuli anterior were shallow. Pupil were dilated, leucorea and pupil reflex were negative. LDH was hight (819 IU/L). CT scan showed right and left retinoblastoma, which spread into the extraconal right orbita, with intracranial structur was normal. Bone marrow aspiration showed non hemopoietic cell (metastatic tumor) and without histopathology or needle biopsi confirmation. The patient was diagnosed with retinoblastoma occuli dextra et sinistra (Bilateral retinoblastoma).**

It is now known that retinoblastoma can be inherited as

a familial tumor in which the affected child has a positive family history of retinoblastoma or as a nonfamilial (sporadic) tumor in which the family history is negative for retinoblastoma. Approximately 6% of newly diagnosed retinoblastoma cases are familial and 94% are sporadic. All patients with familial retinoblastoma are at risk to pass the predisposition for the development of the tumor to their offspring, but the manifestations are only 80% penetrant. Retinoblastoma is generally classified in three different ways: familial or sporadic, bilateral or unilateral, and heritable or nonheritable. About two thirds of all cases are unilateral and one third are bilateral. It is recognized that bilateral and familial retinoblastoma are caused by a germline mutation and are thus a heritable tumor. Unilateral sporadic retinoblastoma is usually not heritable. However, it is estimated that approximately 10% to 15% of children with unilateral sporadic retinoblastoma have a germline mutation.[3,7] The retinoblastoma gene (RB1) maps to locus within q14 band of chromosome 13 and codes for a protein, pRB, that function as supressor of tumor formation. pRB is a nucleoprotein that binds to DNA and control the cell cycle at the transition from the G1 to the s phase, thereby inhibiting cellular proliferation. Genetic counseling testing for retinoblastoma is available but has limitations. Karyotipic studies can identify only large deletions spanning 2 to 5 million base pairs, which account for only 3% - 5% patients. Direct methods using DNA analysis are time consuming and high cost and fail to find the mutation in up to 20% of case.[5] **In our case, there was a positive family history (her father's). Chromosome analysis showed major structure was normal. The patient was diagnosed retinoblastoma bilateral familial nonheritable.**

There are 4 clinical stages of retinoblastoma: intraocular, regional, central nervous system, and hematogenous. The Reese-Ellsworth Classification, developed in 1963, based on intraocular tumor staging and globe salvage prediction after external beam radiation **(Table 1)**. [1,6,7]

Group I consist of eyes with the lowest risk of enucleation and group V with the higest risk. In 2003, a new classification system for intraocular retinoblastoma was finalized **(Table 2)**.[1]

There is seem to be no inherent differences in the risk of metastatic disease between patients with germline mutations and those with sporadic retinoblastoma. Delay in diagnosis is the major risk factor in affecting survival. Kopelman and colleagues[9] reported that the chances of metastasis and death were 2.5 times greater in patients in whom the clinical diagnosis of retinoblastoma was delayed. Metastasis from retinoblastoma typically develops within 1 year after diagnosis of the intraocular tumor retinoblastoma, can spread anteriorly via the vitreous cavity or subretinal space toward the anterior segment, invading the ciliary body and anterior chamber and resulting in a pseudohypopyon. The tumor can extend posteriorly toward the optic nerve with intracranial invasion. Retinoblastoma may invade the orbit directly through the choroid and sclera or by following the scleral emissary canals of the cilliary arteries and nerves. Metastatic dissemination may also occur via lymphatic or vascular pathways. Patients with hereditary retinoblastoma are at risk for developing an intracranial neuroblastic tumor, most often a pinealoblastoma or other parasellar tumor, in the first 5 years of life. This ''trilateral retinoblastoma''is found in approximately 3% of all children with retinoblastoma and 10% of those with bilateral or familial retinoblastoma. The median time from diagnosis of retinoblastoma to the diagnosis of the neuroblastic tumor is 21 months. Unfortunately, pinealoblastoma is almost universally fatal with only

Table 1. Reese-Ellsworth classification

Group 1 :	Very favorable
	a. Solitary tumor, less than 4 disc diameters in size, at or behind the equator
	b. Multiple tumors, none over 4 disc diameters in size, all at or behind the equator
Group II :	Favorable
	a. Solitary tumor, 4 to 10 disc diameters in size, at or behind the equator
	b. Multiple tumors, 4 to 10 disc diameters in size, behind the equator
Group III :	Doubtful
	a. Any lession anterior to the equator
	b. Solitary tumor, larger than 10 disc diameters behind the equator
Group IV :	Unfavorable
	a. Multiple tumor, some larger than 10 disc diameters behind the equator
	b. Any lession extending anteriorly to the ora serata
Group V	Very unfavorable
	a. Massive tumors involving over half retina
	b. Vitreus seeding

Table 2. The international classification of retinoblastoma

Group	Subgroup	Quick reference	Specific feature
A	A	Small tumor	Retinoblastoma ≤3 mm in size
B	B	Large tumor	Retinoblastoma >3 mm in size
		Macula	Macular retinoblastoma location (≤3 mm to foveola)
		Juxtapapilary	Juxtapapillary retinoblastoma location (≤1,5 mm to disk)
		Subretinal fluid	Clear subretinal fluid ≤3 mm from margina
C		Focal seeds	Retinoblastoma with
	C2		Subretinal seeds ≤3 mm from retinoblastoma
	C2		Vitreous seeds ≤3 mm from retinoblastoma
	C3		Both retina and vitreous seeds ≤3 mm from retinoblastoma
D		Difuse seeds	Retinoblastoma with
	D1		Subretinal seeds >3 mm from retinoblastoma
	D2		Vitreous seeds >3 mm from retinoblastoma
	D3		Both retina and vitreous seeds >3 mm from retinoblastoma
E	E	Extensive retinoblastoma	Extensive retinoblastoma occupying >50% globe or neovasculer glaucoma. Opaque media from hemorhage in anterior chamber, vitreous or subretinal space.Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, anterior chamber

*Modified from Murphree and Shields and Shields

a few survivors.[1] **In our case, CT scan showed retinoblastoma extraoccular of the right eye and retinoblastoma intraoccular of the left eye without spread to the Pinealis gland or Parsellar. There was metastatic to the bone marrow. So the patient was diagnosed with group E retinoblastoma or grade V.**

Management of a child with retinoblastoma is individualized and is based on the threat of metastatic disease, risks for secondary cancers, systemic status, laterality of disease, size and location of tumors, anticipated visual prognosis, and response to treatment. The most important objective of a treatment plan is the survival of the child, followed by salvage of the globe, and finally the preservation of the best possible visual function. Chemotherapy alone is not curative and must be combined with intensive local therapy. Several chemotherapeutic agents including methotrexate, cyclophosphamide, triethylenemelamine (TEM), actinomycin, doxorubicin, cyclosporine, etoposide, vincristine, carboplatin and melphalan have been used for retinoblastoma chemotherapy. Chemotherapy is used to shrink the tumor until it is accessible to adjuvant focal treatment such as photocoagulation, thermotherapy, cryotherapy, or brachytherapy. The number and frequency of chemotherapy cycles vary from institution to institution and are dependent on the stage of the tumor. Chemotherapy reduces the size of the tumor but does not usually cure the retinoblastoma, focal therapy is necessary to consolidate the chemotherapy response. Chemoreduction, followed by focal consolidation, has reduced the frequency of enucleation and spared the complications associated with primary EBRT (such as the development of secondary nonocular tumors).[1,3,5,7,10,11] The treatment of bilateral disease is based on the stage of the most advanced eye **(Table 3)**. Bilateral retinoblastoma require enucleation of at least 1 eye in 60% of cases for dangerously advanced tumor. Bilateral enucleation is necessary in only about 1% of cases.[1]

Management of extraoccular retinoblastoma includes intensive multimodality chemotherapy, homologous hematopoetic stem cell rescue, and EBRT. Exenteration is rarely necessary**.** The risk of trilateral retinoblastoma is 5 – 15% in patiens bilateral retinoblastoma. Serial MRIs every 6 months arouse to screen high-risk patient until age 5 years old. Long term disease, disease free-survival is possible if the CNS is not occur. Otherwise the prognosis is usually poor.[5,11] **In our case, management of these patient was primary systemic chemotherapy (chemoreduction) with protocol extraoccular retinoblastoma 2002. Chemoreduction for retinoblastoma have employed cyclophospamide, doxorubicin, vincristin, cytocin arabinase, methotrexate intratecal. After finished chemotherapy intensive phase, proptosis**

Table 3. Treatment strategy on basis of laterality and retinoblastoma grouping (diagnosis, classification, and treatment of retinoblastoma, 2008)

International clasification of retinoblastoma	Unilateral	Bilateral (on the basis of most advance eye)
A	Cryotherapy or laser photocoagulation	Cryotherapy or laser photocoagulation
B	Vincristin, carboplatin plus Thermotherapy/cryotherapy, or plaque radiotherapy	Vincristin, carboplatin plus Thermotherapy/cryotherapy
C	Vincristin, carboplatin plus etopuside plus Thermotherapy/ eryotherapy or plaque proton radiotherapy	Vincristin, carboplatin plus etopuside plus Thermotherapy/cryotherapy
D	Vincristin, carboplatin plus etopuside plus Thermotherapy/ cryotherapy And subconjungtivalcarboplatin, or enucleation	Vincristin, carboplatin plus etopuside plus Thermotherapy/ cryotherapy And subconjungtival carboplatin
E	Enucleation	Enucleation, but if both eyes equally advance then Vincristin, carboplatin plus etopuside plus Thermotherapy/ cryotherapy or plaque or proton radiotherapy

*Modified from Shields and Shields

ofthe right eyes was smaller then before chemotherapy. The patient was still on treatment chemotherapy continous phase.

SUMMARY

In our case, a 3 year old girl with protruding right eyes (proptosis) and shiny white spot or cat's eyes on the left eye. There was history of strabismus on the right eye 1 year before admission, painfull and red eyes, poor vission, and occular inflamation. There was a positive family history (her father's). CT scan showed right and left retinoblastoma, which spread into the extraconal right orbita, with intracranial structur was normal. Bone marrow aspiration showed non hemopoietic cell (metastatic tumor) and without histopathology or needle biopsi confirmation. The patient was diagnosed with retinoblastoma occuli dextra et sinistra (bilateral retinoblastoma) familial. Despite the intensive chemoterapy management, the prognosis of this patient still worse.

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