

## Case Report

# Retinoblastoma or Neuroblastoma: an imaging polemic issues

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## ABSTRACT

Both retinoblastoma and neuroblastoma are common childhood malignancy, which classified as malignant round cell tumors, but have different diagnostic, therapeutic, prognostic criteria and metastases pattern. A case was evaluated with an imaging examination resembled neuroblastoma metastatic process but was diagnosed as retinoblastoma. A 2-years-old boy came with chief complaint swollen right eye. Prior history was itchy and increasingly swollen right eye, decreased vision and gradually increases pain. There was no sign of leukocoria. Histopathology result confirmed malignant round cell tumor. Axial contrast-enhanced head CT image, depicted right intra orbital mass, 1.9x2x1.8 cm in size as well as mass in the right frontoparietal region which pushed the right frontal lobe, accompanied by erosion and periosteal reaction in the surrounding bone with meningeal and soft tissue involvement. In this case, although there was no leukocoria as the diagnostic criteria for retinoblastoma, we still found intraorbital and pineal body mass also malignancies in several long bones. The diagnosis of trilateral retinoblastoma has been established followed by retinoblastoma's chemotherapy regiment, which showed good response, in spite of discrepancy in retinoblastoma's metastases pattern. A complete systemic workup includes CT scan examination needs to be perform in order to help the clinicians determine the diagnosis of orbital mass with malignant round cell histopathology.

**Keywords:** Head computerized tomography, Neuroblastoma, Retinoblastoma

## INTRODUCTION

Both retinoblastoma and neuroblastoma are common childhood malignancy.<sup>1</sup> Retinoblastoma, accounts for 3% from pediatric solid tumors, is a primary intraocular malignancy of the childhood. Mostly unilateral with specific finding of abnormal white reflection from the eye. However, in special case such as trilateral retinoblastoma, abnormalities occurred in both retinal as well as brain primitive neuroectodermal tumor at the midline.<sup>2</sup> While neuroblastoma, incidence rate approximately 8%, is the second most common intra-

abdominal neoplasm with various primary growth and metastases pattern that follow the distribution of sympathetic ganglia.<sup>3</sup> Retinoblastoma and neuroblastoma have similar histopathology appearance, namely malignant small round cell tumor, include others types of tumors such as Ewing's sarcoma, rhabdomyosarcoma, hepatoblastoma, non-Hodgkin's lymphoma, primitive neuroectodermal tumors (PNET) and Wilm's tumor.<sup>4</sup> Ambiguous orbital clinical symptoms, histopathology and metastases pattern, makes it difficult for clinicians to make an assessment and determine further therapy. One case was evaluated with an imaging examination

resembling neuroblastoma metastatic process but was diagnosed as retinoblastoma.

### CASE REPORT

A 2 years old boy came to our institution with chief complaint swollen right eye. Prior history was itchy right eye since January 2019 followed by increasingly swollen eye as the size of marbles, decreased vision, right eye redness and gradually increases pain. There was no sign of abnormal white reflection from the right eye. He undergone several examinations at regional hospital, the diagnosis of retinoblastoma was established based on clinical examination. The right eye continues swollen and reached pingpong ball sized (Figure 1).

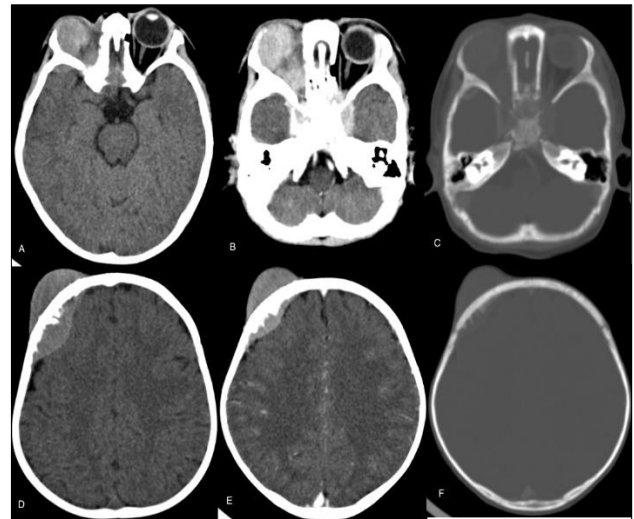


**Figure 1: Clinical presentation. (A) Right orbital swelling since 4 months ago followed by (B) right frontal lump extended to parietal region. (C) The lump also appeared on the left thigh and leg.**

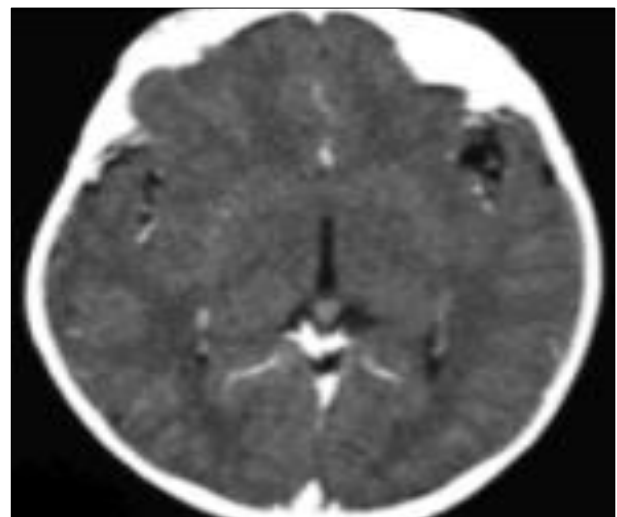
According to the parents, 1 cycle of radiotherapy given approximately 2 months ago, but there was no medical record about the radiotherapy. Then the ocular bulb ruptured and had active bleed thus emergency enucleation performed. Parts ocular tissue were sent to the histopathology laboratory with malignant round cell tumor as a result. The boy also complained lump on the right frontal region expanded to the right parietal region since 1 month ago and also there was left leg and tight swelling with gradually increased pain. After that the boy was referred to our institution for further examination and treatment. Neither initial CT examination before nor complaints on the left eye. There was also progressive weight loss.

At our institution we performed axial contrast-enhanced CT image and figured out right intra orbital mass which has broad-based to the lateral orbital wall approximately 1.9 x 2 x 1.8 cm in size with punctuate calcification. Neither right ocular bulb nor mass expansion to the optic nerve and chiasm which was a typical feature of retinoblastoma. There was also a mass in the right fronto-parietal region which pushed the right frontal lobe, accompanied by erosion and hair on end periosteal reaction in the surrounding bone with meningeal and soft tissue involvement (Figure 2). The pineal body has a slightly bigger in size, approximately 7.30 x 7.08 x 5.81 cm with relatively normal cranial index (Figure 3). We

also found contrast enhancement on the pineal body therefore the possibility of pineal mass still cannot be excluded.

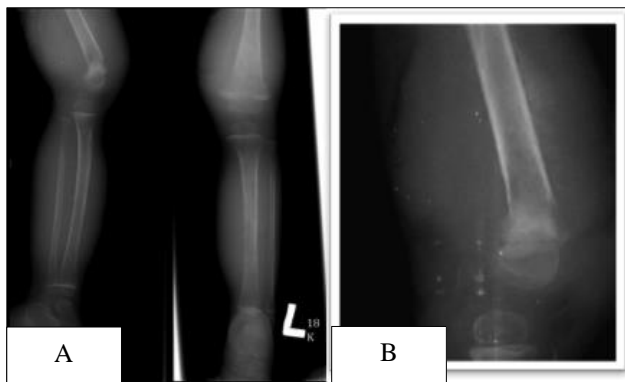


**Figure 2: Axial section contrast-enhanced head CT. (A) Right intraorbital mass which broad based to the lateral orbital wall and (B) enhanced after contrast administration. (C, F) Bone window showed erosion and interrupted periosteal reaction on right zygoma and dan frontal bones. (D, E) There was also meningeal and soft tissue involvement at the right frontal region. There was no evidence of optic nerve and chiasm involvement.**



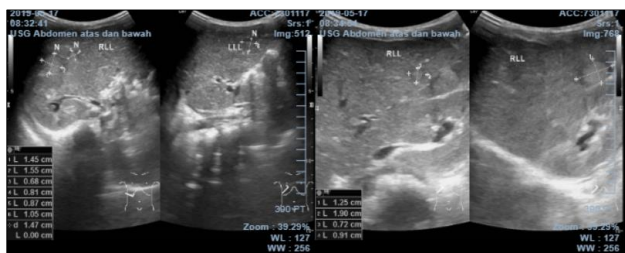
**Figure 3: Pineal body in axial contrast enhanced head CT. Pinal size approximately 7.30 x 7.08 x 5.81 cm with contrast enhancement and relatively normal cranial index.**

In lower limb radiography, we evaluated cortex destruction on left distal third femoral bone and proximal third tibia bone. There was also hair on end interrupted periosteal reaction accompanied with decreased bone trabeculation (Figure 4).

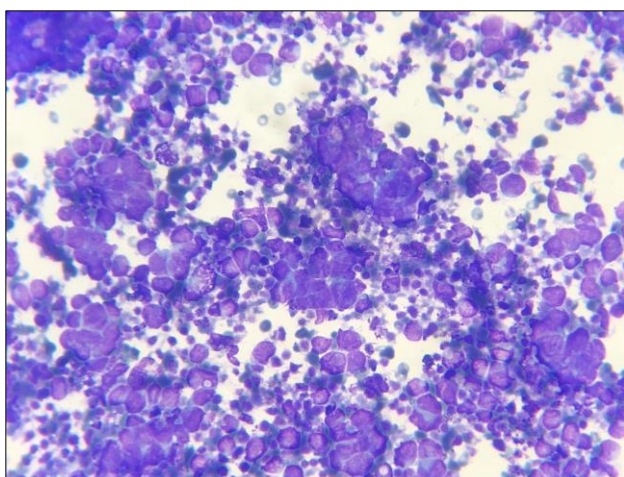


**Figure 4: Left leg radiograph AP and lateral projection. (A) Cortex destruction on left distal third femoral bone and proximal third tibia bone with hair on end interrupted periosteal reaction accompanied with decreased bone trabeculation. (B) Interrupted periosteal reaction of the distal third femoral bone.**

Multiple hyperechoic nodules was found on both liver lobes which varies in size, the presence of retroperitoneal and mediastinal mass still cannot be excluded (Figure 5).



**Figure 5: Abdominal ultrasound. Multiple hyperechoic nodules were seen on both liver lobes. Neither bilateral suprarenal mass nor retroperitoneal mass was visualized.**

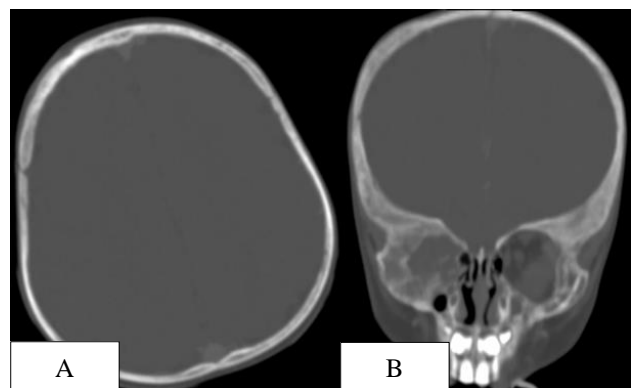


**Figure 6: Cytology examination. The result was malignant round cell tumor. Tissue hypercellularity with diffuse neoplastic cells and Rossette component (Diff. Kwik, x400).**

The lump on the right frontoparietal region got bigger and it also appears in several places during hospitalization such as at the left frontal, forearm and foot. The second histopathology result of right frontal lump was small round blue cell and the third cytology result from FNAB at left frontal, left forearm and left thigh showed round-ovoid cells with narrow basophilic cytoplasm and also round-ovoid, cleaved and moulding nuclei with increased N/C ratio, moderate anisokaryosis, irregular nuclear membrane, hyperchromatic nuclei, inconspicuous nucleoli which arranged in diffuse and Rossette formation. Mytothic phase was easy to find. The background was erythrosit cells (Figure 6).



**Figure 7: Contrast enhanced head CT follow up after 6 cycle of chemotherapy. Right orbital cavity mass with calcified components and the size of the pineal body slightly reduced.**



**Figure 8: Bone erosion. (A) Erosion of the right frontoparietal bone and right zygoma bone, with interrupted periosteal reaction and minimal thickening of the dural layer. (B) Right zygoma bones and right zygomatic arc appeared to be thicker with decreased bone trabeculation.**

The boy got retinoblastoma's chemotherapy regiment (vincristine, etoposide and carboplatin) start from May 2019 and showed a good result marked by reduced periorbital swelling and lump size. Contrast enhanced head CT follow up after 6 cycles of chemotherapy still showed a mass in the right orbital cavity with calcified components that increased in size and shape of



calcifications as well as the size of the pineal which was reduced approximately 7.14 x 6.44 x 5.29 mm accompanied by slightly contrast enhancement (Figure 7).

Right frontoparietal bone and right zygoma bone, still appeared eroded with interrupted periosteal reaction and there was thickening of the dura layer with a maximum thickness of 2.78 mm and contrast enhanced, zygoma bones and right zygomatic arc appeared to be thicker (from 8.51 mm before to 12.38 mm in recent head CT) with decreased bone trabeculation (Figure 8). Radiologically, contrast enhanced head CT scan illustrates the reduction of lesions that show a good chemotherapy response.



**Figure 9: Clinical presentation after 6 cycles of chemotherapy. (A) Swollen left eye with pustule secretion during chemotherapy. (B) After the chemotherapy the left eye return to its normal size, noted the white spot around the sclera.**



**Figure 10: Normal appearance of left optic nerve. Left optic nerve thickness in the orbital, prechiasmatic and optic tract aspects appear normal in width.**

In the middle of the chemotherapy, left eye start swollen and produce pustule secretion, there was no evidence of leukocoria. After the chemotherapy end, the left eye returns to its normal size but the visual function decreased until light perception. Macroscopically, we could see white spot around left sclera (Figure 9).

Neither visible mass nor calcification on the left oculi bulb in contrast enhanced head CT examination, left optic nerve thickness in the orbital, prechiasmatic and optic tract aspects measured 2.88, 2.54 and 3.74 mm respectively, which were normal in size (Figure 10). There was no retrobulbar mass. Left preseptal region thickened with contrast enhancement, which was suggestive for inflammation process although the possibility of left extraoculi mass still could not be ruled out.

## DISCUSSION

A malignant round cell is a very aggressive malignant tumors consist of small and monotonous undifferentiated cells where the nuclear-cytoplasmic ratio found increased. These cells type found in retinoblastoma, neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma, hepatoblastoma, non-Hodgkin's lymphoma, primitive neuroectodermal tumors (PNET) and Wilm's tumor, while a specific type small blue round cell tumor more emphasis on neuroblastoma, rhabdomyosarcoma, non-Hodgkin's lymphoma, Ewing's sarcoma, primitive neuro ectodermal tumor (PNET) and Wilm's tumor.<sup>5</sup>

Retinoblastoma is the most common pediatric intraocular tumor with an incidence of 1:15,000 to 1:18,000 births and the onset of the symptoms mostly appears at the age of 2 years old. Most retinoblastomas occur unilateral (60%) but can also bilaterally, where 0.5% unilateral retinoblastoma develops into trilateral retinoblastoma with median time of transformation is 21 months. Retinoblastoma is curable with adequate therapy as long as the mass within the globe and no sign of metastases. On the other side, trilateral neuroblastoma is a rare case with poor prognosis and the average age at the time of diagnosis was 13 months.<sup>6,7</sup>

While neuroblastoma itself as the second most common intra-abdominal neoplasm with various primary growth and metastases pattern that follow the distribution of sympathetic ganglia. The incidence is 15% and the diagnosis is mostly enforced at the age of 5 and under, the average age was 22 months. As the great imitator, mostly neuroblastoma occur extracranial wherein 40% appear in adrenal gland, followed by 25% of retroperitoneal para spinal ganglia, 15% on mediastinum, 5% on neck and 3% pelvis.<sup>8</sup> Cranial and orbital neuroblastoma's metastases are rare entities, only 10-20% of case metastasize to orbits.<sup>9</sup> The prognosis of neuroblastoma relatively better than trilateral retinoblastoma, about 40% for the long term survival.

Retinoblastoma's symptoms have similarities with neuroblastoma's orbital metastases such as periorbital swelling and decrease visual function. Specific appearance such as raccoon's eyes is more likely described neuroblastoma's metastases pattern.<sup>10</sup> The diagnosis of retinoblastoma is usually established by typical clinical symptom, namely leukocoria which in funduscopic and ultrasound of the eye depicted intra tumoral calcification. Optic nerve involvement is the most important risk factor for CNS metastasis, whereas extra scleral invasion is reported to be the most significant risk factor for distant metastasis as the tumor gains access to vascular and lymphatic channels outside the eye. Other retinoblastoma's metastases distribution includes the orbit, preauricular nodes, bones, central nervous system (CNS) and liver.<sup>11</sup>

Enhanced CT images can be found mass infiltration into optic nerve and chiasma without any periosteal or dural reactions around it. Single or multiple calcifications which vary in size and shape (punctate, nodular, or flocculent) also evaluated on CT image. Intraocular calcifications in a child younger than 3 years old are strongly suggestive of retinoblastoma. As we know for trilateral retinoblastoma, beside leukocoria in both retinal, we must found well defined iso-attenuating mass with marked heterogeneous enhancement and cystic component on pineal body. On MR image we evaluated intracranial or intra spinal leptomeningeal dissemination.<sup>6,11,12</sup>

Trilateral retinoblastoma increased risk of secondary primaries malignancies in bone and soft tissue such as osteosarcoma, leiomyosarcoma, spindle cell sarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, angiosarcoma, Ewing sarcoma, and PNET. Involvement of multiple bones and other tissue would point towards metastases rather than multifocal secondary primary malignancies. Rhabdomyosarcoma and osteosarcoma appearance seems to be the most common second primary neoplasm followed retinoblastoma occurrence. Osseous metastases on trilateral retinoblastoma were reported most commonly in the skull and long bones present with pain, fever and abnormally low blood counts.<sup>6,12,13</sup>

Neuroblastoma metastases pattern through skin, liver, bone marrow, lymph node and hematogenous, not much differ from trilateral retinoblastoma. The orbital metastatic neuroblastoma on enhanced CT scan image shows hyperostosis with hair on end periosteal reaction which distinguish them from retinoblastoma which has more likely lytic with sclerotic margin followed by expansile osseous destruction including epimetaphyses and large soft tissue mass.<sup>12,13</sup> However we have to remember in the cases of retinoblastoma the incidence of osteosarcoma will increase as a secondary malignancy where the radiographs appearance of osteosarcoma is sun burst periosteal reaction that resembles hair on end periosteal reaction.

Abdominal ultrasound evaluation on neuroblastoma shows heterogeneous solid masses that often show calcification. In the adrenal, the mass displaces the kidney inferiorly, encased, stretched, and displaced neighboring vessels also associated adenopathy and/or liver lesions. On CT or MRI scan, we could find large, lobulated, heterogeneous solid mass displacing the adjacent organs, stippled calcification, conglomerate nodal masses with calcification or a paravertebral mass with intra-spinal extension.<sup>14</sup>

In this case, authors observed right eye swelling and redness with itchy and sometimes pain sensation without leukocoria. Right intra orbital mass as well as meningeal and soft tissue involvement with hair on end periosteal reaction on enhanced orbital CT as well as negative secondary findings on the spread of retinoblastoma through the optic nerve and optic chiasm does not decreased the possibility of trilateral retinoblastoma. There were several case report of meningeal involvement of retinoblastoma CNS metastases. Suspicion of pineal mass still cannot be excluded because the pineal body slightly bigger in size, normally (6.1 mm±1.2) x (3.7 mm±0.8) x (4.8 mm±1.1), with contrast enhancement.<sup>15</sup> Multiple nodules on both liver lobes which varies in size also observed without evidence of suprarenal mass. Multiple lump on right bilateral frontal region which expanded into right parietal region, left forearm, thigh, leg and foot wherein the histopathology result was malignant round cell tumor with Rosette's component. In lower limb radiography, we evaluated cortex destruction on left distal third femoral bone and proximal third tibia bone. There was also interrupted periosteal reaction accompanied with decreased bone trabeculation, appropriate with primary malignant bone tumor. Absence of right oculus bulb provides its own obstacles in CT evaluation. The chemotherapy regiment of retinoblastoma showed good result on the patient.

The imaging modality plays an important role in establishing the diagnosis and helping determine the next therapeutic plan and prognosis values. Although enucleation and radiotherapy still used, current selective intra-arterial chemotherapy is the main choice in retinoblastoma's management. Recent chemotherapy protocol used for retinoblastoma are vincristine, etoposide and carboplatin regimens.<sup>16</sup>

## CONCLUSION

In the cases of malignant round cell tumor followed by pineal mass and primary bone tumor with no primary mass founded at the sympathetic ganglia region, trilateral retinoblastoma could be diagnosed, whether there was a meningeal involvement that resembled metastatic neuroblastoma. These facts showed the importance of systemic workup include evaluation of the pineal body, soft tissue and bones, especially contrast enhanced CT image, to distinguished specific type retinoblastoma with

neuroblastoma which is very influential in subsequent management plans.

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