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Case Report

Digital Gangrene and Antiphospholipid Syndrome in a Retinoblastoma Patient with Chromosome 13q Deletion: A Case Report

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Keywords
13q deletion · Retinoblastoma · Digital gangrene · Antiphospholipid syndrome · Paraneoplastic syndrome · Case report

Abstract
A 19-month-old girl with Cornelia de Lange-like dysmorphic features presented with left eye leukocoria. She was diagnosed with 13q deletion retinoblastoma grade 4 with high-risk features and bone marrow involvement. She underwent enucleation, and the first course of intravenous chemotherapy was initiated. On day 10 after the first chemotherapy dose, she developed digital gangrene of her left hand. She was diagnosed with acute artery occlusion and limb ischemia. Thrombophilia work-up revealed antiphospholipid antibodies, and paraneoplastic syndrome is another possible cause of digital gangrene. The patient's left thumb and index finger were amputated. After 1 month of hospitalization, she was discharged. Before the second course of chemotherapy, the patient died of systemic metastatic retinoblastoma with respiratory failure due to pneumonia. Our postulation of the mechanism for digital gangrene was the combination of chemotherapy, paraneoplastic syndrome, and antiphospholipid syndrome. Digital gangrene could be a poor prognostic indicator in patients with retinoblastoma.

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Background

Retinoblastoma is the most common childhood intraocular malignancy [1, 2]. Isolated retinoblastoma develops as a result of biallelic mutations in the tumor suppressor Retinoblastoma gene (*RB1* gene). This gene is located on the long arm of chromosome 13, band 14 (13q14). If there is a deletion on chromosome 13q14, not only the RB1 gene but also other genes in that part are affected. Patients were reported to have dysmorphic features similar to those of Cornelia de Lange syndrome [3].

Digital gangrene most commonly occurs in children as a catheter-related complication [4, 5]. The other causes are sepsis, vasculitis, hypercoagulability [6], paraneoplastic syndrome [7, 8], and chemotherapy [9–11]. To date, the only report on digital gangrene in a patient with retinoblastoma is the one by Das et al. [7]. In Das et al. [7], the patient had advance retinoblastoma, and he developed digital gangrene 10 days after enucleation before staring chemotherapy. All thrombophilia worked up was negative. The paraneoplastic Raynaud's phenomena were the most likely pathogenic mechanisms. Herein, we report a case of a patient with 13q deletion retinoblastoma who developed digital gangrene which accentuates the association between digital gangrene and retinoblastoma. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000530182).

Case Presentation

The patient was a 19-month-old girl with small perimembranous ventricular septal defects and asthma. She had been born following an uncomplicated pregnancy and her family history was unremarkable. Her parents noticed that she had leukocoria for 1 month, and she was diagnosed with unilateral retinoblastoma group E (International Classification) in the left eye. She had Cornelia de Lange-like features (prominent eyebrows with synophrys, upturned nose, long philtrum, thin lips, and hirsutism) [3], developmental delay, midfacial hypoplasia, a short upturn nose, bushy eyebrows, long eyelashes, and a low anterior hairline.

Magnetic resonance imaging confirmed left unilateral retinoblastoma (1.4 × 1.7 × 1.1 cm) with subretinal hemorrhage, no optic nerve involvement, and an unremarkable brain (Fig. 1). Chromosomal analysis revealed 46,XX,del(13)(q12q14) in all 20 GTG-banded cells. The eye was examined under general anesthesia and left eye enucleation was performed (Fig. 2). A pathology report showed a retinoblastoma G4 tumor with poorly differentiated cells with extensive areas of anaplasia, involvement of the vitreous, retina, subretinal space, optic nerve head at laminar cribrosa, and massive choroidal invasion. The optic nerve margin was negative. Bone marrow biopsy revealed a few tiny groups of small round cells (5–10% of the total nucleated marrow cells) that were positive for CD56, synaptophysin, and chromogranin A (Fig. 3). The cerebrospinal fluid analysis, chest X-ray image, and bone scan revealed normal findings. A diagnosis of 13q deletion retinoblastoma grade 4 with high-risk features and bone marrow involvement was made.

One month after the enucleation, adjuvant chemotherapy was administered with vincristine, etoposide, and carboplatin. On day 8 after the first dose of chemotherapy, the patient showed up in the emergency room with respiratory failure and her nasal swab was positive for respiratory syncytial virus. She was diagnosed with respiratory syncytial virus pneumonia requiring endotracheal intubation. She was administered intravenous fluids and piperacillin-tazobactam via a cannula on her right hand. She was successfully extubated after 5 days of intubation, and ventolin and budesonide were used for supportive treatment. On day 10 after the first dose of chemotherapy, her left fingertips turned pale and her left wrist pulse became

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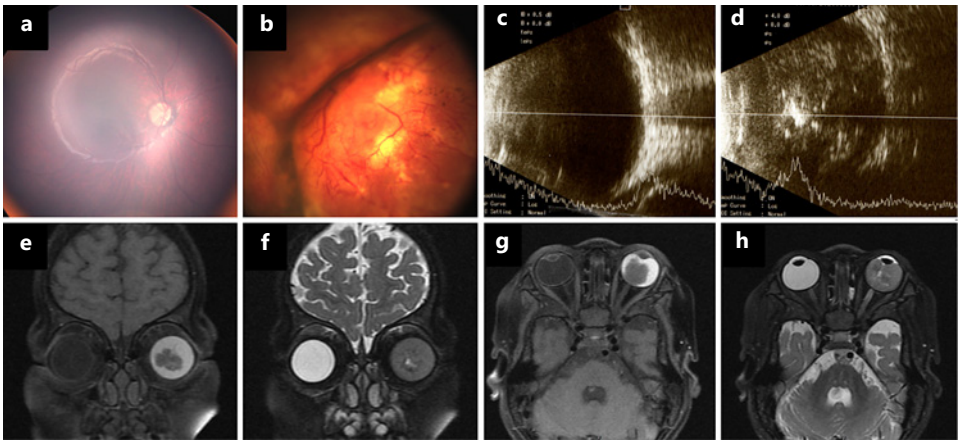

Fig. 1. Unilateral retinoblastoma in the left eye. Fundus photo: **a** right eye, **b** left eye; ultrasonography: **c** right eye, **d** left eye; **e** coronal T1 magnetic resonance imaging (MRI); **f** coronal T2 MRI; **g** axial T1 MRI; and **h** axial T2 MRI.

absent. Doppler ultrasound examination revealed normal flow of the brachial artery, decreased flow of the radial artery, and absent flow of the ulnar artery. No blood clot was seen. The patient was diagnosed with acute artery occlusion with ischemia of the left hand. Heparin was administered intravenously, and it was switched to enoxaparin 3 days later. The hemoculture showed no growth after 7 days. Echocardiography showed a small perimembranous ventricular septal defect of 3 mm, but no aortic regurgitation, pulmonary stenosis, or blood clots. Thrombophilia work-up revealed a high titer of anticardiolipin (aCL) IgM and anti-beta-2-glycoprotein I (B2GPI) IgM. The aCL IgG and B2GPI IgG levels were normal. Lupus anticoagulant (LAC) was detected using the diluted Russel Viper Venom Time (dRVVT) test. Antithrombin III, protein C, and protein S levels were normal. Acute limb ischemia due to antiphospholipid syndrome was suspected.

The fingertips and left thumb were erythematous and swollen, and muscle necrosis or wound infection was suspected. Vancomycin was added to piperacillin/tazobactam. Repeat Doppler ultrasound on day 15 of admission showed recanalization and detected pulses from the brachial, radial, and ulnar arteries. Finally, the fingertips and the left thumb became gangrenous (dry gangrene). On day 29 of admission, the left thumb and index finger were amputated, as shown in Figure 4. After 1 month of hospitalization, the patient was discharged on oral cephalexin and subcutaneous enoxaparin. The second course of chemotherapy was postponed until the wound healed.

Three months later, there was a repeat measurement of the antiphospholipid autoantibody level. The aCL IgG/IgM and anti-B2GPI IgG/IgM levels were normal, but LAC was still detected. Antiphospholipid syndrome was confirmed due to the persistence of antiphospholipid autoantibody, and enoxaparin was continued. The amputation wound healed and skin grafting and the second course of chemotherapy were planned. Before the second course of chemotherapy, the patient showed up at the emergency department with anorexia and dyspnea. Her parents opted for palliative treatment, but she died due to metastatic retinoblastoma.

Discussion and Conclusions

The mortality rate of retinoblastoma varies from 3 to 70%, depending on the economic status of the country, stage of the disease at diagnosis, accessibility to an eye-cancer center,

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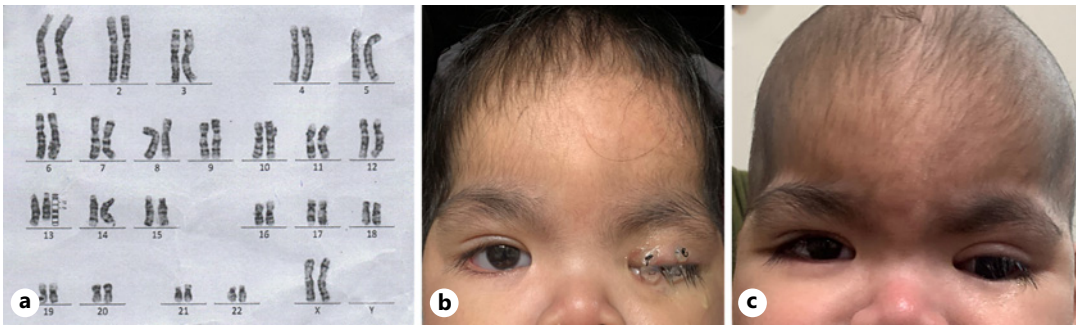

Fig. 2. a Karyotype analysis showed deletion of long arm chromosome 13. **b** Facial appearance after enucleation with temporary tarsorrhaphy. **c** Facial appearance after enucleation with ocular prosthesis implantation.

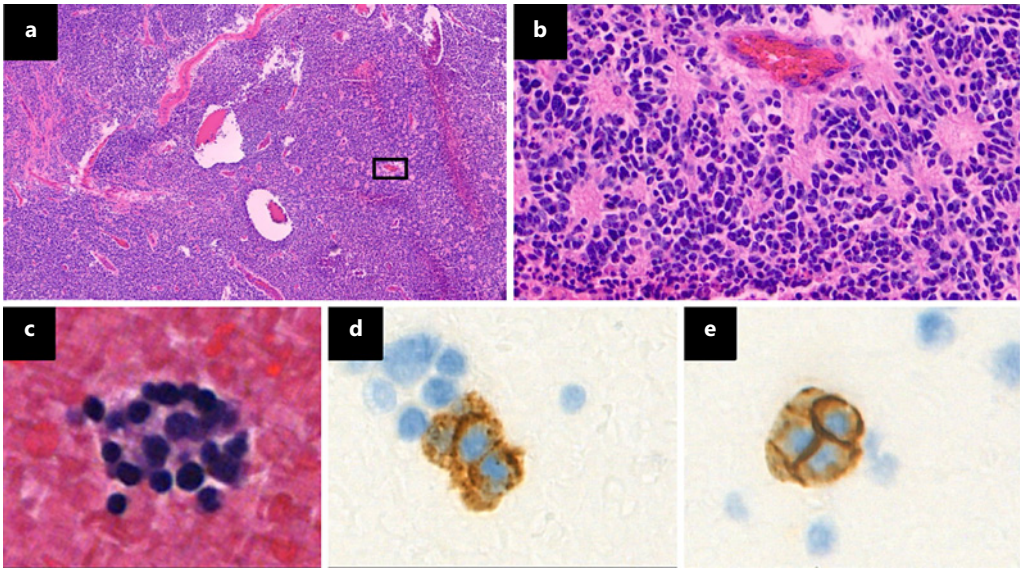

Fig. 3. Histopathology of ocular and bone marrow tissue. **a** Ocular tissue with H&E stain ×5. **b** Ocular tissue with H&E stain ×40. **c** Bone marrow tissue with H&E stain ×100. **d** Bone marrow tissue with synaptophysin stain ×100. **e** Bone marrow tissue with CD56 stain ×100. The ocular sections reveal retinoblastoma tumor with poorly differentiated cells with extensive areas of anaplasia. The bone marrow sections reveal tiny groups of small round cells that were positive for CD56 and synaptophysin.

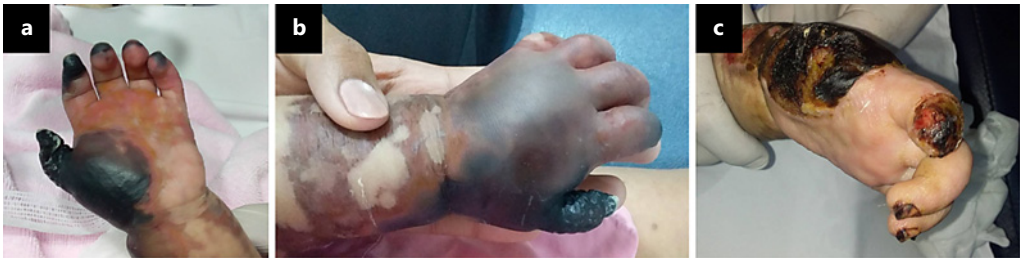

Fig. 4. Digital gangrene of the left hand. **a**, **b** Before amputation. **c** After amputation.

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histopathology, genetic background, and socioeconomic factors [1, 12]. This patient presented to the hospital with advanced retinoblastoma. She also had dysmorphic features similar to those of Cornelia De Lange syndrome. Karyotyping may help rule out chromosome 13q14 deletion in patients with Cornelia De Lange-like features. It was reported that 90–95% of patients with deletions on chromosome 13q14 have retinoblastoma [3]; therefore, they should be referred to an ophthalmologist for retinoblastoma screening.

The current treatment modalities are cryotherapy, transpupillary thermotherapy, enucleation, chemotherapy (intravenous, intravitreal, and intra-arterial), external beam radiotherapy, and plaque radiotherapy [1, 2, 7]. This patient had high-risk features of unilateral retinoblastoma with bone marrow involvement and required intravenous chemotherapy post-enucleation. She received vincristine, etoposide, and carboplatin, a standard regimen for retinoblastoma. The side effects of this regimen, such as alopecia, cytopenia, and fever, are usually minor [1, 2]. However, there have been few reports of digital gangrene following cisplatin-based chemotherapy in the treatment of other types of malignancy [9, 10, 13]. The pathogenesis of thrombosis due to cisplatin-based chemotherapy remains unclear, but the potential mechanism involves vascular endothelial damage and induction of a hypercoagulable state [9, 10].

Paraneoplastic syndrome is another possible cause of digital gangrene. Several mechanisms have been postulated, including vasospasm from sympathetic hyperactivity due to metastatic tumors invading sympathetic nerves [8], vasculitis, hyperviscosity, and hypercoagulability [7, 8]. There are few reports about paraneoplastic syndrome in retinoblastoma patients [14, 15]. The patient described in the report by Das et al. [7] also had paraneoplastic syndrome presented with digital gangrene in advanced retinoblastoma, like the one in this report. Both of them died within 6 months after the onset of digital gangrene.

A previous study on pediatric antiphospholipid syndrome revealed that 4 out of 121 patients (3%) presented with digital gangrene and 1 out of 121 patients (0.8%) were associated with malignancy [16]. A systematic review of 2,773 patients with solid tumors and antiphospholipid (aPL) antibody-related thromboembolic events showed an increased risk of antiphospholipid antibody-level elevation in patients with solid cancers [17]. Our patient had evidence of arterial occlusion with persistent elevation of the antiphospholipid antibody level after 12 weeks, and a definitive diagnosis of antiphospholipid syndrome was made.

This is the first report of digital gangrene in pediatric antiphospholipid syndrome with a solid malignancy. Our postulation of the mechanism of the digital gangrene in this patient was a combination of chemotherapy, paraneoplastic syndrome, and antiphospholipid syndrome. Digital gangrene and antiphospholipid syndrome underlying it could be a poor prognostic indicator in patients with retinoblastoma.

Acknowledgements

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Statement of Ethics

Ethics approval and consent to participate was approved by the research Ethics Review Committee of Queen Sirikit National Institute of Child Health, the approval reference number

is REC.125/2021 on Oct 11, 2021. Written informed consent was obtained from the parents for publication of this case report and any accompanying images.

Conflict of Interest Statement

Nutsuchar Wangtiraumnuay, Supawan Surakrattanaskul, and Chonthida Wangkittikul declare that they have no competing interests.

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Author Contributions

Nutsuchar Wangtiraumnuay: conception and design, acquisition of data, analysis and interpretation, drafting and revising, and final approval. Supawan Surakrattanaskul: acquisition of data, drafting and revising, and final approval. Chonthida Wangkittikul: acquisition of data, analysis and interpretation, drafting and revising, final approval.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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