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Leukemia Misdiagnosed Clinically as Suspected Abusive Head Trauma

A medical examiner's office in another state forwarded a pair of postmortem eyes from a 3 month-old baby boy to our laboratory for histopathologic assessment. The eyes were forwarded because abusive head trauma was suspected.

According to the ME's records, the patient's mother stated that the baby began developing shortness of breath thought to be due to a respiratory infection at the end of November 2017. The mother also stated that the infant had been taken to the doctor multiple times.

On January 15, 2018 the family called 911 because the baby was having difficulty breathing. A team of paramedics responded to the call and decided that the parents could take the infant to the hospital on their own. They took him to a hospital ER at 9 P.M. that evening. The chief complaints were shortness of breath, vomiting and diarrhea for two days. The child was afebrile. He was discharged home after receiving a breathing treatment. Discharge diagnoses were nasal congestion and diarrhea. A screen for respiratory syncytical virus (RSV) was negative.

At 6:30 AM that morning, the father was holding the baby when it appeared that it was about to vomit. According to the parents, as the father rushed into the bathroom the baby's head struck frame of the bathroom door. The baby cried-out, but was soothed by the father. He did not lose consciousness. That evening, the mother informed the ER doctor about the bruise on the infant's head during the visit to the hospital. The doctor said it appeared OK. No x-rays or CT scans were done. Medical records of the ER visit reviewed by the ME showed no evidence of any laboratory testing besides the RSV screen.

On January 16, the Police Department received another 911 call from same residence that stated that the infant was not breathing. The paramedics brought the decedent to the hospital in cardiac arrest. The hospital staff noted bruising and swelling on the left side of the head. A postmortem CT scan showed bilateral subarachnoid hemorrhages, greater on the left side. This presumably led to the suspicion of child abuse and AHT.

Significant autopsy findings included a linear contusion on the lateral left side of the head. No skull fractures were present. There was a diffuse subarachnoid hemorrhage on the left cerebrum less than 1 mm thick and a focal subarachnoid hemorrhage on the right temporal lobe. Hepatomegaly, splenomegaly and a bilateral pleural effusion were present. At the present time (July 11, 2018) microscopic sections from the autopsy have not been reviewed. The infant was not known to have Noonan Syndrome or NF1

Gross description: (right eye)

The right eye measured 19 x 18.5 x 18 mm and had 20 mm of optic nerve attached. The optic nerve was removed and multiple transverse sections were made. A small amount of blood is seen within the optic nerve sheath in several of the sections. The globe was opened horizontally. The lens showed posterior umbilication. Severe postmortem autolytic changes were present. These included extensive sloughing and dispersion of the retinal pigment epithelium. The retina was totally detached with numerous nonspecific folds. No retinal hemorrhages were seen grossly. The PO segment and the transverse sections of the optic nerve were submitted for routine sections.

Gross description: (left eye)

The left eye measured 18.5 x 18 x 19 mm and had 23 mm of optic nerve attached. The optic nerve was removed and multiple transverse sections were made. A small amount of blood was seen within the nerve sheath in several of the sections. The globe was opened horizontally. The lens showed posterior umbilication. Postmortem autolytic changes were evident as sloughing and dispersion of the retinal pigment epithelium. The retina was totally detached with numerous nonspecific folds. No retinal hemorrhages were seen grossly. The PO segment and multiple transverse sections of the optic nerve were submitted for routine sections.

Microscopic Description (right eye)

Microscopic examination disclosed a postmortem globe with severe postmortem autolytic changes. These included detachment and focal disruption of the corneal endothelium, extensive detachment and sloughing of the retinal pigment epithelium, degeneration of the peripheral lens cortex, detachment of the lens capsule and subtotal artifactitious detachment and fragmentation of the neurosensory retina. The lens showed posterior umbilication consistent with the patient's age. Numerous dyscohesive atypical cells with round nuclei, irregular nuclear contours, prominent nucleoli and scant to moderate amounts of cytoplasm, consistent with leukemic blasts were seen within choroidal and retinal vessels, as well as vessels in the soft tissues of the orbit and extraocular muscles. In addition, a significant extravascular deposit of cells was present anteriorly within the epibulbar tissues. Rare retinal hemorrhages were present. Microscopic examination of transverse sections of orbital optic nerve submitted separately showed varying numbers of leukemic cells within the optic nerve sheath as well as the soft-tissue and vessels of the orbit. In some areas a modest amount of blood was mixed with the leukemic cells within the nerve sheath.

Diagnosis:
Right postmortem eye showing extensive involvement by leukemic cells (see comment).

Microscopic Description: (left eye)

Microscopic examination of the PO segment prepared from the left globe revealed a postmortem globe with severe postmortem autolytic changes. Similar to the right eye, there was extensive involvement of ocular and adnexal tissues by leukemic

cells. These formed prominent extracellular deposits in epibulbar tissues and also filled the lumina of retinal and choroidal vessels. An extensive focus of cells was present within the vitreous cavity. Leukemic cells also were seen within the optic nerve sheath, in the central retinal vessels, and in the orbital soft-tissue in the sections of transversely sectioned orbital tissue submitted separately. Small amounts of blood were present within the nerve sheath adjoining the leukemic cells.

Diagnosis:
Left postmortem eye showing extensive involvement of eye and orbital tissues by leukemic cells (see comment).

Comment

Immunohistochemical stains, performed with appropriate controls on PO segments of the right and left globes showed that the atypical cells were immunoreactive for CD33 and CD45 (diffuse), CD14 (subset), CD163 (subset), myeloperoxidase (subset), lysozyme (subset), and were negative for CD34, CD43, CD117, CD4, CD56, PAX5, CD3, and TdT. The Ki-67 proliferative index was approximately 40% in the better preserved regions of the tumor. The slides were reviewed in consultation with Dr. Adam Bagg, Hematopathology Department of the Hospital of University of Pennsylvania. Dr. Bagg thought that the combined morphologic and immunohistochemical findings were compatible with extensive involvement of ocular and orbital tissues by leukemia, possibly juvenile myelomonocytic leukemia. Additional molecular genetic studies required for definitive characterization of the leukemia were not performed.

Discussion

Postmortem examination of a pair of eyes from a 3 month-old Hispanic infant suspected of having abusive head trauma disclosed that the infant actually had previously undiagnosed leukemia, possibly juvenile myelomonocytic leukemia. No significant retinal hemorrhages or characteristic retinal folds were identified. Minor amounts of blood in the optic nerve sheath were associated with leukemic cells.

The infant purportedly had developed shortness of breath attributed to a respiratory infection approximately 6 weeks previously, and had been taken to the doctor multiple times. One day prior to death, he was evaluated in a hospital emergency room for shortness of breath, vomiting and diarrhea. He was afebrile and was discharged after a breathing treatment with the diagnoses of nasal congestion and diarrhea. The only laboratory test performed was an RSV screen. A CBC was not performed and the child was not imaged. The child died at home the next day and was returned to the hospital by paramedics. Concern for AHT was raised by a linear scalp contusion that had been noted during the prior ER visit. According to the parents, this was sustained when the infant's head struck the frame of the bathroom door while he was being carried by the father during an attack of vomiting. Preliminary results of a postmortem exam disclosed hepatomegaly, splenomegaly and a bilateral pleural effusion as well as thin subarachnoid hemorrhages. The diagnosis of leukemia had not been suspected prior to our examination of the post-mortem eyes.

Ocular involvement is relatively common in leukemia, especially the acute leukemias. In 1983, Marilyn Kincaid and W. Richard Green reviewed the ophthalmic findings in 384 pairs of post-mortem eyes from patients with leukemia. 233 of the patients had acute leukemia of whom 82% had ocular involvement. 75% of 97 patients with chronic leukemia had some type of ocular involvement. Retinal hemorrhages are

relatively common finding in leukemic eyes and may include white centered hemorrhages resembling Roth spots with a central nidus of leukemic cells. Choroidal infiltration is also common. Vitreous infiltration unassociated with vitreous hemorrhage is rare, as are microaneurysms and peripheral neovascularization. The latter typically occur in patients with chronic leukemia. Anterior segment involvement, also rare, can manifest as iris heterochromia or a yellowish-white pseudohypopyon of leukemic cells.

The classification of leukemia has become increasingly complicated in recent years. Recent modfications of the WHO classification recognize nearly 30 categories of acute myeloid leukemia including nine variants distinguished by recurrent genetic abnormalities including translocations or mutations. The patient presented here is thought to have juvenile myelomonocytic leukemia (JMML), but there is no specific immunophenotype for that disorder and the additional molecular genetic tests required for definitive diagnosis were not performed.

Classified as a myelodysplastic or myeloproliferative disorder by the WHO, JMML typically affects children age 4 years or younger. The average age at diagnosis is 2 years and about 10% of cases are diagnosed before 3 months of age. JMML is quite rare, comprising only 1-2% of cases of childhood leukemia yearly in the United States (25-50 new cases; 3 cases per million). The 5 year-survival of untreated JMML is only 5%. The only effective therapy is hematopoietic stem cell transplantation with a survival rate of approximately 50%. There is a high risk of relapse after stem cell transplantation.

There are interesting associations between JMML and several other disorders. About 14% of children with JMML have clinically diagnosed NF1 and up to 30% have mutations in the NF1 gene. Noonan syndrome (NS) also predisposes to the development to JMML or a myeloproliferative disorder that resembles JMML. The latter is found in the first weeks of life and may resolve spontaneously. Noonan syndrome, which has also been called male Turner Syndrome or female pseudo-Turner syndrome is an autosomal dominantly inherited syndrome caused by heterozygous mutation in the PTPN11 gene on chromosome 12q24. The child presented here was not known to have NF1 or NS.

Gross and microscopic examination of both postmortem eyes from this case disclosed no convincing evidence of abusive head trauma. There were no significant retinal hemorrhages or characteristic retinal folds and no significant optic nerve sheath hemorrhage. The relatively small amount of blood found within the optic nerve sheath was mixed with leukemic cells. The lumina of retinal and choroidal vessels were dilated and filled with leukemic cells. Choroidal vessels were similarly involved and an extensive infiltrate of leukemic cells was present in the substantia propria of the conjunctiva. In addition, a significant infiltrate of leukemic cells mixed with blood was present in the vitreous of the left eye. The latter did not resemble vitreous hemorrhage as leukemic cells were the predominant component of the vitreous infiltrate. A battery of immunohistochemical stains was consistent with, but not diagnostic of JMML.

Characteristic features of abusive head trauma found histopathologically include retinal hemorrhages that are often too numerous to count and may extend to the ora serrata. The retinal hemorrhages include deep and superficial retinal hemorrhages and focal round or oval convex hemorrhagic detachments of the ILM, which had been termed "cherry hemorrhages". Characteristic retinal folds thought to be caused by vitreoretinal traction also are typically observed. These include a perifoveal ridge that surrounds the macula. Detachment of the internal limiting membrane, which typically involves the posterior retina, is another characteristic feature. Unfortunately, the latter feature usually is called retinoschisis in the AHT literature. Although most eyes have an artifactual retinal detachment, focal collections of blood occasionally are found in the subretinal space. Optic nerve sheath hemorrhage is another important and characteristic feature of

AHT. In cases with severe optic nerve sheath hemorrhage, the nerve often appears blue or purple grossly. The greatest amount of blood typically is found in the ampulla of optic nerve sheath directly behind the globe, an observation that suggests that the blood does not enter the orbital nerve sheath from the CNS. The blood in the optic nerve sheath can be located in the subdural and/or subarachnoid spaces and often infiltrates the collagenous dura in severe cases. Other characteristic findings observed occasionally include hemorrhage in the juxtapapillary sclera and orbital fat and rarely the extraocular muscles.

Recently, there has a great deal of unwarranted controversy in the lay media about AHT or shaken baby syndrome (SBS). The latter includes articles in the New York Times and Forbes magazine, a report on NPR, a highly criticized dissenting opinion by Justice Ginsburg in a US Supreme Court case and a highly touted and favorably reviewed documentary film called "The Syndrome". The documentary claims that SBS is based on "junk science", has led to the incarceration of innocent parents and caregivers and is promoted by greedy physicians. In the legal arena, unscrupulous physicians who profit from providing "expert testimony" for defendants attribute the signs of AHT/SBS to a variety of nontraumatic causes and conditions. These include birth trauma, rebleeding of occult subdural hematomas, subdural hematomas due to hypoxia, venous sinus thrombosis, relatively minor "short falls", benign external hydrocephaly, vaccinations, paroxysmal coughing and choking, and a variety of systemic, metabolic and heritable disorders that include von Willebrand diease, Vitamin K deficiency, Hermansky Pudlak Syndrome, Ehlers-Danlos Syndrome, glutaric acidura type I, Menkes Syndrome, osteogenesis imperfecta and "temporary brittle bone disease".

In recent years, I have examined a significant number of cases of eyes from children suspected have having AHT that are submitted to our laboratory by the Philadelphia Medical Examiner's Office. Stereotypical findings typically are observed in these postmortem eyes from infants who usually have other characteristic non-ocular signs of non-accidental trauma including sub-dural hematomas, skull and long bone fractures and other signs of abuse. Fortunately, I do not have the burden of testimony; the latter is done by Dr. Alex Levin, Chief of the Pediatric Ophthalmology and Ocular Genetics Service at Wills, a noted expert on child abuse and AHT.

In most instances, alternate explanations cited by "hired gun" defense attorneys in AHT/SBS cases are totally spurious and represent true "junk science". However, the case presented here shows that in rare instances, parents can be falsely suspected of child abuse when their child succumbs to a disorder that is unsuspected and undiagnosed.

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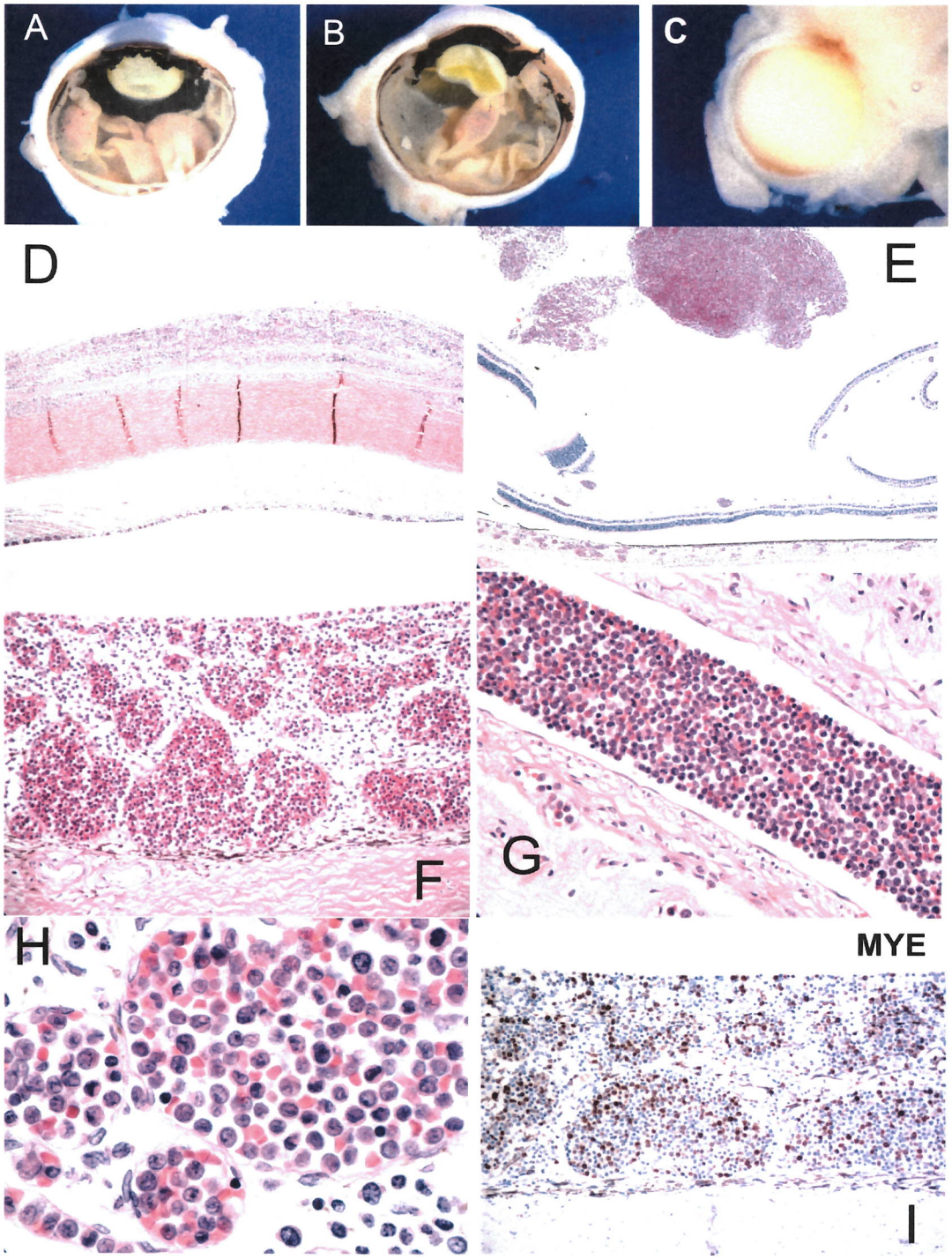

A, B. Severe postmortem autolysis; no retinal hemorrhages C. Mild hemorrhage in optic nerve sheath D. Infiltrate of leukemic cells on epibulbar surface and vitreous (E) F. Leukemic cells in choroidal vessels and CRA (G) H. Blasts in choroidal vessels I. Positive immunoreactivity for myeloperoxidase