In 1998, Mary Ella Pierpont first described 2 unrelated boys (9 and 2.5 years of age) with remarkably similar facial dysmorphism, plantar fat pads on hands and feet, and global developmental delay. The facial features were unique in that both patients displayed midface hypoplasia, anteverted nostrils, a central palatal ridge, and an elevated forehead together with mild microcephaly. Plantar fat pads were described as deep grooves generating the appearance of “pillowing” pads between the grooves. Severe speech delay was demonstrated in both patients; the 9-year-old boy was unable to speak.

Since that time, only 1 other case has been reported in which an identical triad of peripheral characteristics occurred. The physical examination findings were accompanied by findings of MR spectroscopy of the brain in which the early clinical developmental delay was associated with an increased choline peak in the frontal white matter zones. In both reports, no cytogenetic aberrations were detected in lymphocytes or skin fibroblasts, and analyses ruled out chromosomal mosaicism and mucopolysaccharidoses. It remains unclear whether the inheritance pattern resembles an autosomal dominant or x-linked recessive pattern.

Here, we report the case of a 6-month-old boy diagnosed with Pierpont syndrome; this is only the fourth patient described in the scientific literature and the first documented case of an oncological process—an intraventricular atypical choroid plexus papilloma tumor—found in association with Pierpont syndrome. Syndromes associated with choroid plexus papilloma are reviewed.

Case Report

History and Examination. This 6-month-old male infant presented with a history of progressively increasing head circumference, bilateral hearing deficit, and acute onset of sunsetting eyes. He had been eating and
drinking well, but had recently appeared lethargic to his parents. His family history was unremarkable; 2 older siblings (male and female) and parents in the 5th decade of their lives were in good health. He was born after a full-term pregnancy that was complicated by preeclampsia and was noted to have a patent ductus arteriosus that closed later than expected. Physical examination revealed a Caucasian male with macrocephaly, prominent anterior fontanel, midface hypoplasia with a central palatal ridge, and thickened plantar folds on his feet and hands (Fig. 1). He could spontaneously roll from side to side without turning over and was able to interact socially to some degree.

An initial noncontrast head CT scan demonstrated a large hyperdense mass within the left lateral ventricle that was associated with gross panventriculomegaly with greater prominence in the supratentorial triventricular system than the fourth ventricle (Fig. 2). Magnetic resonance imaging demonstrated a hyperintense, pedunculated mass measuring approximately 5.2 × 4.2 × 2.8 cm, located posteriorly in the choroid plexus of the left lateral ventricle, along with diffuse ventriculomegaly (Fig. 2). Due to his presenting symptoms and hydrocephalus, an emergency placement of a right frontal external ventricular drain was performed, and the patient was subsequently taken to the operating room for neuroendoscopic resection of the intraventricular mass.

**Operation.** The patient was brought to the operating room and intubated after airway protection was established and an external ventricular drain was placed. A left-sided superior parietal craniotomy was followed by an endoscope-assisted resection of the tumor. Through the endoscope, we cauterized the choroid plexus, and after the tumor was resected (without the endoscope), we used the neuroendoscope to confirm tumor resection and hemostasis. During resection, the mass itself appeared quite vascular, and results from examination of the specimen that was sent for intraoperative analysis confirmed tumor pathology consistent with CPP. The tumor was resected in its entirety. Postoperatively, the hydrocephalus persisted and required permanent ventriculoperitoneal shunting.

**Pathological Examination.** Examination of H & E–stained sections showed branching fibrovascular fronds with either single cuboidal or columnar cells lining the outer perimeter (Fig. 3 left). Ki 67 staining revealed increased mitotic activity with a proliferative index of approximately 30% (Fig. 3 right). These findings were suggestive of an atypical CPP (WHO Grade II). Cytogenetic analysis using fluorescence in situ hybridization was unremarkable, and there was no evidence of trisomy 8.

**Postoperative Course.** The boy’s postoperative course was uncomplicated, and the ventriculoperitoneal

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**Fig. 1.** Photograph of the patient demonstrating phenotypic characteristics of Pierpont syndrome, including a central palatal ridge (A), midface hypoplasia (C), and plantar lipomatosis (B and D).

**Fig. 2.** Noncontrast head CT scan (A) obtained on arrival in the emergency department demonstrating gross panventricular hydrocephalus and a large pedunculated hyperdense lesion within the left lateral ventricle. Additionally, mild herniation of the brain at the anterior fontanel and (B) partial agenesis of the vermis can be seen. Postcontrast T1-weighted Gd-enhanced axial (C) and sagittal (D) MR images demonstrate this pedunculated intraventricular mass arising posteriorly with hyperintense signal. The lesion measured 5.2 × 4.2 × 2.8 cm.

**Fig. 3.** Histopathology of the intraventricular mass. **Left:** H & E stain demonstrates branching fibrovascular fronds with single cuboidal or columnar cells. **Right:** Ki 67 staining demonstrates increased mitotic activity. Original magnification ×40.
Choroid plexus papilloma and Pierpont syndrome

shunt (small Strata valve) was maintained at a setting of 1.0. Given that gross-total resection of this atypical CPP had been achieved, the child did not require radiotherapy or chemotherapy and instead underwent observation. At 1-year follow-up imaging, he remained free of any evidence of residual or recurrent disease. At 3 years of age, however, he tested 3 standard deviations below normal development in all cognitive and motor examinations. He communicates with giggles and grunts and does not use words. He is able to sit unassisted for short periods and demonstrates a few upper-extremity activities such as page turning and bell ringing.

Discussion

This case report describes a child diagnosed with Pierpont syndrome associated with an oncological process. This 2.5-year-old boy first presented at the age of 6 months with hydrocephalus due to an intraventricular CPP. In addition, he was found to have prominent facial dysmorphism, medial planar lipomatosis, and developmental delay. Only 3 cases in two cited reports have identified this as Pierpont syndrome. No associated oncological pathology was discerned. Because gross-total resection of the brain tumor did not reverse the clinical signs of Pierpont syndrome, it is difficult to identify a direct causal relationship. Interestingly, Pollack et al. observed a direct syndromic association when a 2-year-old boy presented with head tilt and anteroposterior head bobbing that regressed after resection of a CPP. However, in our case, the presentation of an intraventricular tumor during infancy suggests congenital development in an MCA/MR syndrome. In this light, it is possible that amplification of abnormal genetic loci suggests that Pierpont syndrome represents a cancer predisposition syndrome, and in this case was associated with the CPP.

Syndromic association with choroid plexus tumors is not novel. In fact, a growing body of single-case reports has suggested associations with monosomy 1p36 and with Costello, Li Fraumeni, Aicardi, and von Hippel-Lindau syndromes. There are more than 700 MCA/MR syndromes documented by the US National Library of Medicine. Monosomy 1p36 is one MCA/MR syndrome also found in association with a choroid plexus anomaly (choroid plexus hyperplasia) and is characterized by congenital heart defects, developmental delay, precocious puberty and deletion of 1p36.33 Our patient was also documented to have a congenital heart defect with delayed closure of the patent ductus arteriosus, but further presented with phenotypic characteristics of Pierpont syndrome and without identified genetic deletions. Phenotypic features of Costello syndrome are similar, given the developmental delay and extra skin folds, but also include joint hypermobility, HRAS genetic association, and adult onset of CPP presentation. Given the early presentation in our case, Pierpont syndrome may act as a cancer predisposition syndrome similar to Li Fraumeni; however, that it has an autosomal dominant pattern of familial expression and the fact that is often found with TP53 and CHEK2 genetic abnormalities weigh against this. All reported Pierpont cases have been identified in boys, which argues against the possible association with Aicardi syndrome, an x-linked dominant inheritance pattern commonly found in girls. Choroid plexus papilloma has been observed in association with another CNS-related vascular tumor presenting in von Hippel-Lindau syndrome. Interestingly, cytogenetic studies were unremarkable in our case, unlike the genetic abnormalities listed in the above CPP-associated syndromes.

Choroid plexus tumors represent an uncommon intracranial tumor, having an incidence of 0.3%–0.7% and constituting 3%–6% of brain tumors in the very young (less than 36 months of age). These tumors are of neuroepithelial origin and arise intraventricularly, generally in the choroid plexus of the lateral, third, and fourth ventricles in children. The most common histological grade is the papillomatous form (WHO Grade I), which arises more frequently in infancy. However, the high-grade carcinomatous form occurs more frequently than WHO Grade II atypical CPP. Concern for a genetic derivation and association with various syndromes is not unreasonable, considering the predominant presentation in infancy, which suggests a congenital origin.

Our findings suggest that a child presenting with the triad of phenotypic characteristics of Pierpont syndrome should be evaluated for intraventricular tumors, especially when presenting with macrocephaly rather than associated mild microcephaly. The histological aberrancy seen here provides comparative assessment to other CPP-associated syndromes. As it is in the other syndromes associated with CPP, resection remains the standard of care when symptomatic presentation appears. Characterization of the case reported here and comparisons to the related syndromes discussed may help to provide further insight into Pierpont syndrome and to develop treatment paradigms that may prove pragmatic.

Conclusions

This is the first report to identify atypical CPP in a patient with Pierpont syndrome. This is the fourth reported case of a child with Pierpont syndrome. Further characterization and long-term follow-up may help identify specific genetic abnormalities and clarify cancer predisposition associations.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Vadivelu, Mittler. Acquisition of data: Vadivelu, Edelman, Schneider. Analysis and interpretation of data: all authors. Drafting of the article: Vadivelu, Edelman, Mittler. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Vadivelu. Study supervision: Mittler.

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