Published in final edited form as:

Pediatr Dev Pathol. 2011 ; 14(1): 71–74. doi:10.2350/10-01-0776-CR.1.

Hepatic Hemangioendothelioma Presenting as Sudden Unexpected Death in Infancy: A Case Report

Johan Dempers, M.B.Ch.B., F.C. For. Path. (S.A.), Dip. For. Med. (S.A.), CML (Unisa)¹, Shabbir Ahmed Wadee, B.Sc., M.B.Ch.B., M.Med.(For Path.), F.C. For Path.(S.A.)¹, Theonia Boyd, MD², Colleen Wright, M.D., M.Med. (Anat. Path.), F.C. Path. (S.A.), F.R.C.Path., F.I.A.C., Ph.D.³, Hein J Odendaal, M.B.Ch.B., M.Med., F.C O.G.(S.A.), FRCOG, MD⁴, Mary Ann Sens, MD, PhD⁵, and the PASS Network⁶

¹Division of Forensic Medicine and Pathology Department of Pathology and Western Cape Forensic Pathology Services Faculty of Health Science, Stellenbosch University Tygerberg, South Africa

² Department of Pathology Children's Hospital Boston Harvard Medical School Boston, MA 02115

³Division of Anatomical Pathology Department of Pathology and NHLS Tygerberg Faculty of Health Science, Stellenbosch University Tygerberg, South Africa

⁴Department of Obstetrics and Gynecology Faculty of Health Science, Stellenbosch University Tygerberg, South Africa

⁵Department of Pathology University of North Dakota School of Medicine and Health Sciences 501 N Columbia Road Grand Forks, ND 58202

⁶The PASS Network members are listed in the acknowledgments section.

Abstract

The classification of an unexpected infant death as the sudden infant death syndrome (SIDS) depends upon a complete autopsy, death scene investigation and review of medical history to exclude known causes of death. Death from occult neoplastic disease in infancy is extremely rare but is within the broad differential of SIDS. We report the sudden and unexpected death of a one-month-old infant from a hepatic (infantile) hemangioendothelioma. The physiologic mechanism of death was likely cardiac failure induced by the circulatory demands of this large vascular tumor and respiratory compromise from diaphragmatic thoracic incursion. The clinical progression and pathology of these relatively common tumors of infant livers are extremely variable. This case dramatically illustrates the potential for fatal outcome of this tumor, as well as the need for the autopsy to determine the cause of sudden and unexpected death in an infant

Keywords

Autopsy; death scene investigation; hepatic neoplasms; heart failure; Sudden Unexplained Death in Infancy

Introduction

Sudden unexpected death in infancy (SUDI) has an extremely broad differential in both manner and cause of death. Numerous natural disease processes, including infections, metabolic, genetic and developmental processes; environmental hazards; unintentional and volitional actions of others may all produce, singularly or in combination, the sudden and unexpected death of an infant. The sudden infant death syndrome (SIDS) is defined as the sudden death of an infant less than a year that remains unknown after a complete autopsy, death scene investigation and review of medical history. SIDS currently accounts for 50-80% of the cases of SUDI deaths^{1, 2, 3}. Although there has been significant progress in the understanding of the underlying pathophysiological mechanisms through knowledge gained from autopsy and scene investigations, pre- and post-natal risk factors, and environmental stressors, SIDS remains a major cause of infant mortality worldwide, across all demographic strata. Clinical investigations and research into sudden deaths in infancy involve multiple avenues in an attempt to identify pre- and post-natal risk factors with the goal of reducing infant mortality. We are involved in the Safe Passage Study of the Prenatal Alcohol in SIDS and Stillbirth (PASS) Network, a federally-funded, prospective study of 12,000 women and their infants to determine the relationship between prenatal alcohol exposure, stillbirth, and SIDS. The PASS Network study populations include the north central United States, primarily North and South Dakota and Cape Town, South Africa, where the SIDS incidence in the mixed ancestry (coloured) is among the highest in the world (3.41/1000 live births)⁴, compared to the overall rate of 0.57/1000 in the United States⁵. We report here a case of sudden death in an infant in the PASS Network which was consistent with SIDS on demographics and death scene investigation but in whom there was a large hepatic hemangioendothelioma which caused the infant death.

Case Report

A one-month-old male infant was found dead in bed by his 24-year-old G2P2A0 mother. The infant was born at full term (40 weeks gestation) by uncomplicated vaginal delivery. The birth weight was 1990 grams (below 3rd percentile) with Apgar scores of 9, 10, and 10 at 1, 5 and 10 minutes, respectively. After routine immunization for tuberculosis and polio, both mother and infant were discharged from the hospital in good condition. The mother smoked approximately 10 cigarettes per day but had no other complications or co-morbidities. The mother breast-fed the infant for two weeks and then changed to formula feeding.

During the two days prior to the death of this infant, the mother noted a runny nose, mild wheezing and diarrhea in the infant. These symptoms improved with over-the-counter remedies, but he appeared less alert and slept more. The mother reported that he seemed

“fussy” on the day prior to his death but fed well and, aside from sleeping more, did not appear ill.

A forensic autopsy was ordered and the parents gave permission for additional tissue procurement for PASS research. A death scene investigation was performed at time of death. On the night of the demise, the infant shared the double bed with a soft foam rubber mattress with his father and mother, sleeping on the side of the bed closest to his mother. The infant was put to bed in the prone position, no pillow, facing the side and was found in the same position.

At autopsy, the 2100 gram, 50.5 cm infant had mild peripheral edema, manifested by swollen eyelids. No evidence of traumatic injury, hemangiomas or other congenital abnormalities of the skin was noted. Multiple tumor nodules up to 2 cm in size were present throughout the liver (Figure 1). There were petechiae on the visceral pleura, epicardium, and thymus (Figure 1). Microscopic sections of the liver neoplasms (Figure 2) showed an infiltrative, richly vascular tumor with dilated vascular channels of varying caliber, lined by a single layer of endothelial cells surrounded by loose connective tissue. The endothelial lining cells were plump with regular, round to ovoid nuclei separated by loose connective tissue. There were no areas of significant fibrosis, thrombi, bile pooling, calcification or myxoid change. Mitotic figures were very scarce. The lungs demonstrated extensive congestion, pulmonary edema and hemosiderin laden macrophages, but no signs of pneumonia or metastases. Subpleural and septal petechial hemorrhages were present; mild prominence of the dilated pulmonary vasculature was present. Maturation age of the lungs was appropriate with well formed alveoli. The 25 gram heart was dilated with tense, blood filled chambers, particularly on the right side; numerous petechiae and focal hemorrhage was also present within the epicardium. There was marked congestion of the small blood vessels but no alterations in myocyte structure. Intense congestion was appreciated in the red pulp of the enlarged spleen (52 gm) and to a lesser extent in the adrenal medulla and kidneys. Thymic petechiae were present and Hassel corpuscle bodies appeared increased in number and size but the cortico-medullary junction was distinct and the cortex was well populated with lymphocytes without a starry sky infiltrate. There was mild lipid depletion of the adrenal cortex. The costo-chondral junction and bone marrow were normal in histologic sections. The remaining organs, including the brain, were unremarkable.

Discussion

Death from an unsuspected neoplasm is very uncommon in infants and children⁶. Overall, liver tumors in this age group account for 1-4% of the solid tumors^{7,8} but death from liver tumors, particularly clinically unsuspected tumors, are extremely rare. In infants, hepatoblastomas and hemangioendotheliomas are the most common malignant and benign tumors, respectively. Hepatocellular carcinoma (HCC), hepatic adenoma, and focal nodular hyperplasia occur most frequently in older children^{7,8}. In South Africa (SA), there is an increased incidence of HCC in young children⁹ which may be decreasing since the introduction of routine HBV vaccination¹⁰.

Infantile hemangioendothelioma is the most common hepatic neoplasm in the first year of life and has a wide spectrum of clinical manifestations¹¹, radiologic signs¹² and pathologic findings¹³. These tumors may be single or multifocal and although many are small, asymptomatic, incidental lesions, larger tumors may produce more significant clinical findings including abdominal distension, failure to thrive, congestive cardiac failure, and bronchiolitis. Anemia is present in half the cases; the incidence of hyperbilirubinemia or elevated liver function tests was 21% and 32%, respectively¹³. Clinical management of these tumors varies with tumor size and symptoms; small tumors may be conservatively watched for spontaneous tumor regression. Treatment options include radiation, surgical resection, corticosteroids or alpha 2A-interferon, and/or arterial ligation or embolization, with survival rates exceeding 80%¹⁴.

Histologic findings of these tumors consist of vascular channels lined by a single layer of plump endothelial cells ("Type 1" lesion) in a supporting fibrous connective tissue stroma. In 50 - 60% of cases, larger vascular channels resembling cavernous hemangiomas may be found as well as areas of calcification, fibrosis and infarction. Mitotic activity is infrequent. Foci of extramedullary hematopoiesis are often reported. True capsules are absent but the tumor margins are well demarcated in 65% of cases¹³. Hemangiomas elsewhere on the body, usually the skin, are reported in 11% of the cases in the largest study¹³ although smaller studies report higher associations. In 20% of the cases, the vascular spaces may be more poorly formed, lined by larger, pleomorphic and hyperchromatic cells, often with tufting or branching ("Type 2" lesions). Prognostic implication of these histologic variants is controversial; some authors believe there is minimal prognostic value in the histologic variants¹³; however others believe the "Type 2" lesions, especially when accompanied by cutaneous hemangiomas, may be indistinguishable from hepatic angiosarcoma¹⁵. Our case had features diagnostic of infantile hepatic hemangioendothelioma, Type 1. There were no other congenital abnormalities noted, specifically there were no cutaneous hemangiomas.

Serious clinical manifestations of hepatic infantile hemangioendotheliomas include atrioventricular shunting with high output, right-sided congestive heart failure; Kasabach-Merritt syndrome from platelet trapping within the tumor vascular channels with resulting thrombocytopenia; mass effect of tumor with respiratory compromise, abdominal or biliary obstruction from tumor compression; or rupture of the tumor with hemoperitoneum¹¹⁻¹³. Large tumors may function as arteriovenous or arterioportal shunts leading to congestive heart failure or portal hypertension^{13, 14}. Most deaths from these tumors occur within the first month after diagnosis¹³; covariates with a poor prognostic value include congestive heart failure at presentation, jaundice, multiple tumor nodules and the absence of cavernous differentiation. Our case had multiple tumor nodules and acute congestive cardiac changes at autopsy, but jaundice was not present.

We attributed the cause of death as cardiac failure from high-output cardiac demands of this large vascular tumor which is capable of producing arteriovenous and arterioportal shunting. Left-sided congestive cardiac failure was also present as manifested by passive congestion of multiple organs with hemosiderin laden macrophages in the lungs, splenomegaly and mild facial edema. This bulky abdominal tumor likely produced a degree of restrictive diaphragmatic excursion; atelectasis was present at autopsy, however maturation of the

lungs was appropriate with well formed alveoli suggesting that significant compromise during fetal development did not occur and the restrictive thoracic component was a secondary consideration to the cardiac failure. There were some anatomic markers of chronic stress with a mild increase in Hassall thymic corpuscles and mild lipid depletion of the adrenals, however the costro-chondial junction was unremarkable and cortex of the thymus distinct and well populated with lymphocytes. Although signs of congestive heart failure and abdominal distention may have been recognized on a routine well baby check, the death occurred prior to a normal visit schedule. Clinically, there was no suspicion of illness in this infant by the parents, thereby mimicking the typical picture of SIDS with only minimal, non-specific findings of “fussiness”, increased sleep and mild upper respiratory symptoms, all commonly seen in infants at this age. The circumstances of death were further typical of SIDS with discovery in bed after a sleep period. The co-sleeping requires consideration of an asphyxial mechanism of death. Cultural and economically necessary co-sleeping is nearly universally present within this child's community. Death scene re-enactment and careful questioning by forensic investigators did not reveal any evidence of asphyxia wedging or overlaying. Although the sleeping circumstances preclude definitive complete elimination of an asphyxial component, we believe the anatomic findings of this massive tumor congestive failure documented at autopsy establishes this tumor as the cause of death. Without an autopsy, this death may have been misclassified as a SIDS death, highlighting the critical importance of a complete autopsy in all unexpected pediatric deaths.

Acknowledgments

We appreciate the help of Dr. Hannah C. Kinney, Brad B. Randall and Rebecca Folkerth in the preparation of this manuscript. Non-author members of the PASS Network Steering Committee (in alphabetical order) are Larry Burd, Ph.D.; Kimberly A. Dukes, Ph.D.; Amy Elliott, Ph.D.; William P Fifer, Ph.D.; Rebecca Folkerth, M.D.; Gary Hankins, M.D.; Dale Herald, M.D., Ph.D.; Hannah C. Kinney, M.D.; Michael M Myers, Ph.D.; Caroline Signore, M.D., M.P.H.; Lisa M. Sullivan, Ph.D. and Marian Willinger, Ph.D.

Acknowledgments

Funding/Support: This research was funded by the following grants from the National Institute on Alcohol Abuse and Alcoholism and the Eunice Kennedy Shriver National Institute of Child Health and Human Development: U01 HD055154, U01 HD045935, U01 HD055155, U01 HD045991, and U01 AA016501.

References

1. Willinger M, James LS, Catz C. Defining the sudden infant death syndrome (SIDS): Deliberations of an expert panel convened by the National Institute of Child Health and Development. *Pediatr Pathol.* 1991; 11:677–78. [PubMed: 1745639]
2. Center for Disease Control (CDC). Sudden Infant Death Syndrome (SIDS) and Sudden Unexpected Infant Death (SUID): Sudden, Unexpected Infant Death (SUID) Initiative. Atlanta, GA, USA: <http://www.cdc.gov/SIDS/SUID.htm> Last accessed: March 18, 2010
3. Krous HF, Beckwith JB, Byard RW, Rognum TO, Bajanowski T, Corey T, Cutz E, Hanzlick R, Keens TG, Mitchell EA. Sudden infant death syndrome and unclassified sudden infant deaths: a definitional and diagnostic approach. *Pediatrics.* 2004; 114:234–8. [PubMed: 15231934]
4. Molteno CD, Ress E, Kibel MA. Early childhood mortality in Cape Town. *S Afr Med J.* 1989; 75:570–4. [PubMed: 2727857]
5. Mathews TJ, MacDorman MF. Infant mortality statistics from the 2005 period linked birth/infant death data set. *Natl Vital Stat Rep* 2008. 57:1–32.

6. Krous HF, Chadwick AE, Isaacs H Jr. Tumors associated with sudden infant and childhood death. *Pediatr Dev Pathol.* 2005; 8:20–5. [PubMed: 15803214]
7. Meyers RL. Tumors of the liver in children. *Surg Oncol.* 2007; 16:195–203. [PubMed: 17714939]
8. Finegold MJ, Egler RA, Goss JA, Guillerman RP, Karpen SJ, Krishnamurthy R, O'Mahony CA. Liver tumors: pediatric population. *Liver Transpl.* 2008; 14:1545–56. [PubMed: 18975283]
9. Moore SW, Millar AJ, Hadley GP, Ionescu G, Kruger M, Poole J, Stones D, Wainwright L, Chitnis M, Wessels G. Hepatocellular carcinoma and liver tumors in South African children: a case for increased prevalence. *Cancer.* 2004; 101:642–9. [PubMed: 15274079]
10. Moore SW, Davidson A, Hadley GP, Kruger M, Poole J, Stones D, Wainwright L, Wessels G. Malignant liver tumors in South African children: a national audit. *World J Surg.* 2008; 32:1389–95. [PubMed: 18305988]
11. Iyer CP, Stanley P, Mahour GH. Hepatic hemangiomas in infants and children: a review of 30 cases. *Am Surg.* 1996; 62:356–60. [PubMed: 8615561]
12. Burrows PE, Dubois J, Kassarian A. Pediatric hepatic vascular anomalies. *Pediatr Radiol.* 2001; 31:533–45. [PubMed: 11550763]
13. Selby DM, Stocker JT, Waclawiw MA, Hitchcock CL, Ishak KG. Infantile hemangioendothelioma of the liver. *Hepatology.* 1994; 20:39–45. [PubMed: 8020903]
14. von Schweinitz D. Management of liver tumors in childhood. *Semin Pediatr Surg.* 2006; 15:17–24. [PubMed: 16458842]
15. Nord KM, Kandel J, Lefkowitz JH, Lobritto SJ, Morel KD, North PE, Garzon MC. Multiple cutaneous infantile hemangiomas associated with hepatic angiosarcoma: case report and review of the literature. *Pediatrics.* 2006; 118:907–913.

1. In situ liver tumor and thoracic cavity. Note the multiple tumor nodules and enlargement of liver which nearly fills the abdominal cavity. Thymic and pleural petechiae are also present.

2.

A) Liver tumor with infiltrating borders, low power, H and E (100x)

B) Cavernous vascular channels were present focally within the tumor mass. Low power H and E (100x).

C) Plump, bland endothelial cells lining tumor vascular channels. High power, H and E (400x).