CASE REPORT

R. W. Byard,[1] *M.D.; J. Schliebs,*[1]*; and B. A. Koszyca,*[1] *Ph.D.*

Osler-Weber-Rendu Syndrome—Pathological Manifestations and Autopsy Considerations

REFERENCE: Byard RW, Schliebs J, Koszyca BA. Osler-Weber-Rendu syndrome—pathological manifestations and autopsy considerations. J Forensic Sci 2001;46(3):698–701.

ABSTRACT: An 18-year-old university student with Osler-Weber-Rendu disease collapsed in the bathroom. Attempted resuscitation was unsuccessful. Her past history included recurrent epistaxes, mucosal telangiectasias, intracranial arteriovenous malformations with previous hemorrhage, a single pulmonary arteriovenous malformation, recent onset of grand mal seizures, and depression. There was a positive paternal family history. At autopsy the pulmonary arteriovenous malformation was confirmed. In addition, within the brain there were widespread areas of gliosis with hemosiderin deposition and small vascular malformations. No other significant abnormalities were detected and toxicological screening revealed only moderately elevated levels of carbemazepine. Death was attributed to epilepsy associated with glial scarring from previous microhemorrhages. The detection of vascular malformations in the lung or brain at autopsy should prompt careful examination of all tissues for similar lesions. Given the possibility of Osler-Weber-Rendu disease in such cases, fibroblast cultures should be undertaken to enable molecular studies to proceed. The heritable nature of this disorder necessitates accuracy of diagnosis at autopsy; once the diagnosis is confirmed family screening should be recommended.

KEYWORDS: forensic science, Osler-Weber-Rendu disease, sudden death

Osler-Weber-Rendu disease, also known as hereditary hemorrhagic telangiectasia, is an inherited condition in which vascular malformations are found in a variety of organs and tissues. The disorder represents a group of autosomal dominant conditions (1) characterized by alterations in growth factor receptors in endothelial cells which result in disturbances of vascular development and function (2). Clinical manifestations often involve spontaneous hemorrhage commonly resulting in epistaxis or hemoptysis (3). Sudden and unexpected death is, however, a rarely reported event in patients with this disorder. The following case demonstrates a variety of issues that may arise in the autopsy assessment of such cases.

Case Report

An 18-year-old university student collapsed early one morning in the bathroom. Attempted resuscitation was unsuccessful. Her past history included Osler-Weber-Rendu disease with recurrent epistaxes since infancy, mucosal telangiectasias, and recent onset of grand mal seizures.

At the age of 13 years, during hospitalization for the investigation of confusion, vomiting, visual loss, and right sided weakness, a large left-sided occipital hemorrhage and two intracerebral arteriovenous malformations were revealed. A craniotomy was performed with evacuation of the hematoma, followed by subsequent radiotherapeutic obliteration of the vascular malformations. She recovered with a minimal expressive dysphasia and right inferior homonymous quadrantopia. Subsequent imaging studies of the brain revealed no vascular anomalies. Coil embolization of an asymptomatic pulmonary arteriovenous malformation performed a little over a year later was only partially successful.

Three months prior to death the deceased suffered a grand mal seizure, followed by several similar episodes which were witnessed by hospital staff. An electroencephalograph demonstrated epileptiform activity in the left parieto-occipital region. In addition, depression and panic attacks were diagnosed. Antidepressant medication was prescribed as well as the antiepileptic drug carbemazepine. Following further probable seizures, the dosage of carbemazepine was increased approximately five weeks before death and cerebral imaging studies were ordered.

There was a strong family history of Osler-Weber-Rendu disease with the father of the deceased having a congenital hemiparesis with numerous truncal telangiectasias and a cerebrovascular accident at the age of 32 years. (It was only after this intracranial episode that Osler-Weber-Rendu disease had been considered.) His grandfather, great-grandmother, two uncles, a first cousin, and four siblings also had manifestations of the disorder. The younger sister of the deceased subsequently developed epistaxis and oral telangiectasias.

At autopsy the body was that of a well developed young adult female of around the stated age of 18 years. No skin telangiectases were observed and although a small amount of blood was present in the right nostril, no nasal mucosal telangiectases could be seen using an otoscope. (The blood may therefore have been caused by trauma during attempted resuscitation.) The bladder was empty and the tongue had not been bitten. No hemorrhage was found in any body cavity or within the gut. The deceased had been menstruating.

A previous left sided craniotomy site was demonstrable and the brain was externally unremarkable apart from patchy hemosiderin staining of the frontal lobes. Formal neuropathological evaluation subsequently revealed a small vascular malformation of the left middle frontal gyrus (Figs. 1,2), old cortical scarring of the right

[1] Forensic Science Center, Department of Pathology, and Medical School, respectively, University of Adelaide, Adelaide, Australia.

Received 13 June 2000; accepted 19 July 2000.

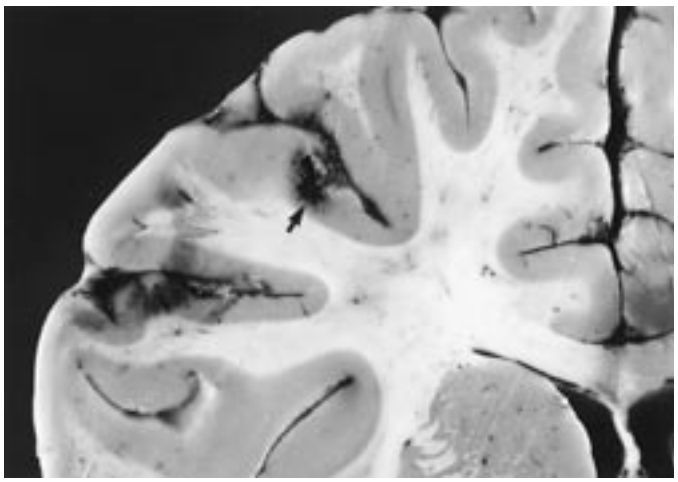

FIG. 1—*Coronal section of the left frontal lobe showing a cortical vascular malformation (arrow). Other dark areas are due to artefactual blood staining from sectioning.*

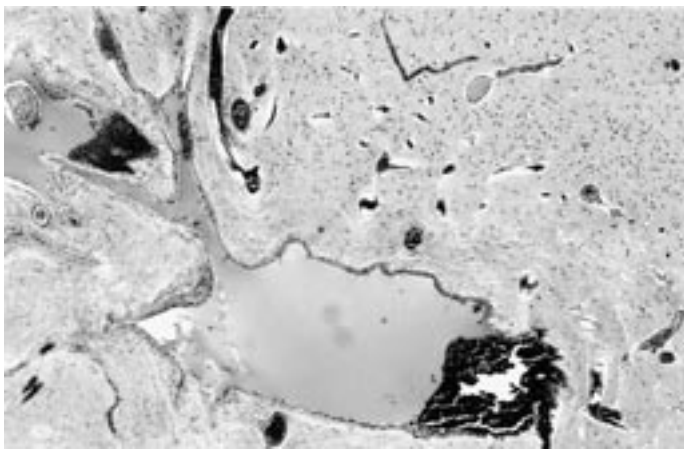

FIG. 2—*Section of the left frontal cortex shown in Fig. 1 demonstrating irregularly dilated vascular spaces (Hematoxylin and eosin × 60).*

Discussion

Criteria for the clinical diagnosis of Osler-Weber-Rendu disease vary slightly, with certain authors making the diagnosis when two of the following three criteria are met: spontaneous epistaxis more than three times per month, mucocutaneous telangiectasia, and an affected parent (5). Others require three of four criteria which include recurrent spontaneous epistaxis, telangiectasias at typical sites, a visceral manifestation, and an affected first degree relative (2). In the reported case all four criteria were met; the presence of lesions in the father of the deceased, and in a large number of paternal relatives in keeping with autosomal dominant transmission. The reported incidence varies between studies from 1 to 20 per 100 000, depending on the population examined (2,6).

The underlying lesion in Osler-Weber-Rendu disease is a defect in vessel walls which causes dilatation of postcapillary venules which may become markedly ectatic and convoluted. Telangiectatic venules may connect to dilated arterioles, or larger vessel communication may occur with direct arteriovenous shunting (1). The skin, mucous membranes, brain, lung, and alimentary tract are most of-

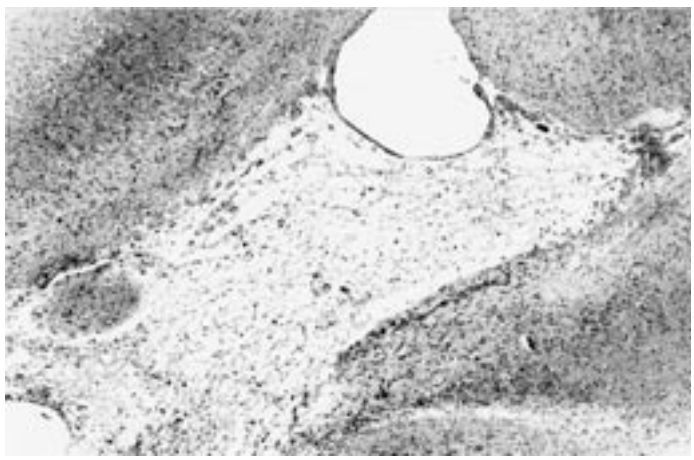

FIG. 3—*Section of the left occipital lobe showing extensive areas of gliosis and cystic necrosis (Hematoxylin and eosin × 60).*

posterior middle frontal gyrus, gliosis of the central white matter of the left temporal lobe, a vascular malformation of the leptomeninges over the left parietal lobe, and old cystic necrosis in the periventricular white matter of the left occipital lobe (Fig. 3).

The only other abnormality found was in the upper portion of the lower lobe of the left lung where an arteriovenous malformation was detected containing coiled wire from a previous attempt at embolization (Fig. 4). Histologically, adjacent arterioles showed organized thrombi. No macroscopic or microscopic abnormalities were detected in the liver, gastrointestinal tract, spleen, or other organs.

Blood toxicological screening revealed an elevated level of carbemazepine (blood level = 19 mg/L; therapeutic level = 4.5 to 12 mg/L). Although the lethal range has been reported above 25 mg/L, individuals have survived levels as high as 77 mg/L (4). No other drugs were detected in the blood.

Death was, therefore, attributed to an epileptic fit, given the clinical history of recent grand mal seizures and the neuropathological findings of widespread areas of glial scarring, particularly involving the left temporal lobe.

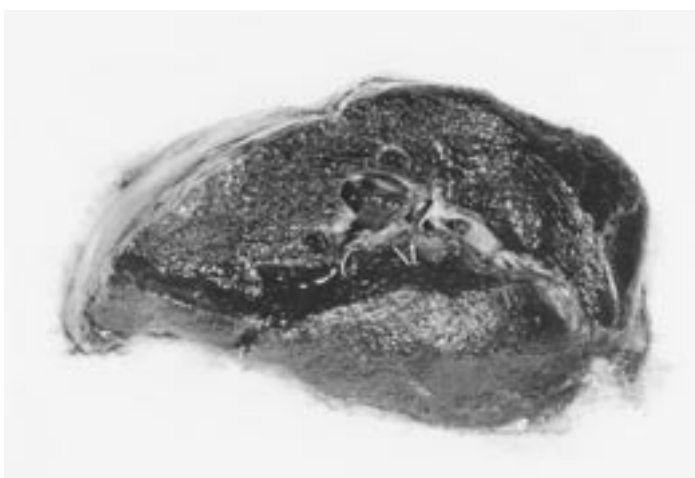

FIG. 4—*Section of the upper portion of the lower lobe of the left lung demonstrating an arteriovenous malformation in which lies a coiled embolising wire.*

ten involved, however, any tissue may be affected, and aneurysms of the aorta and coronary arteries have been reported (3).

Molecular studies have isolated at least two genetic defects in Osler-Weber-Rendu disease. In Osler-Weber-Rendu-1 the mutation is in a locus on chromosome 9q3, which codes for the protein endoglin, and in Osler-Weber-Rendu-2 the defective locus is on chromosome 12q, resulting in defects in the activin receptor-like kinase 1 gene (5,7). Both are highly expressed in endothelial cells and are involved in the binding of transforming growth factor-beta. Although it is known that transforming growth factor-beta influences the composition and organization of extracellular matrix and effects the proliferation, migration, and adhesion of endothelial cells (1), the precise mechanism by which the reported gene defects result in the pathological manifestations of Osler-Weber-Rendu disease remain unclear.

Clinical manifestations involve a variety of different organ systems. Recurrent epistaxis, as in the present case, is often an early manifestation (8). Telangiectasias of the skin tend to appear at a later age (1) and very rarely episodic bloody tears have been reported (2).

Involvement of the brain occurs in 5 to 10% of affected individuals, although the true incidence may be much higher if asymptomatic individuals are investigated (2). Intracerebral vascular malformations may result in hemorrhage, or in ischemia or epilepsy from a vascular steal phenomenon (2). Rarely symptomatic vascular malformations may occur within the spinal cord (9).

Twenty percent of cases demonstrate pulmonary vascular malformations which may bleed or cause high output cardiac failure due to right-to-left shunting. Pulmonary lesions are found more often in females (7). Paradoxical embolism to the brain from pulmonary vascular malformations may result in embolic strokes, or in brain abscesses in 5 to 9% of patients (3). Sixty percent of individuals with pulmonary arteriovenous malformations have Osler-Weber-Rendu disease (1). Both pulmonary and cerebral lesions were demonstrated in the reported case.

Gastrointestinal mucosal telangiectasias are not uncommon in affected individuals but usually do not cause significant bleeding until the fifth or sixth decade (1). Quite severe iron deficiency anemia may occur later in life from chronically bleeding lesions. Liver involvement may consist of scattered telangiectases, with or without fibrosis, discrete massive arteriovenous malformations, or telangiectasia-associated fibrosis ("pseudocirrhosis") (5,10). High-output cardiac failure may also result from hepatic arteriovenous malformations (1). Lesions within the kidneys, bone, and larger vessels are usually asymptomatic (7) and may only be detected at autopsy if meticulous dissection is undertaken.

While it has been asserted in relatively recent texts that individuals with Osler-Weber-Rendu disease usually have a normal life expectancy (11), studies have shown an increased mortality, particularly in those with severe symptoms at an early age (6). Sudden death is, however, unusual and may be associated with massive pulmonary, gastrointestinal, or intracerebral hemorrhage (Table 1).

TABLE 1—*Possible causes of unexpected death in Osler-Weber-Rendu disease.*

Lungs:	pulmonary hemorrhage
GI tract:	gastrointestinal hemorrhage
Brain:	intracranial hemorrhage
	brain abscess
	epilepsy

Pulmonary hemorrhage may occur at any age (12), but presents a particular problem during pregnancy (6). Although intracranial vascular malformations are a recognized cause of unexpected death in the young (13) and may cause hemorrhagic infarction, as in the current case, they have not been reported as a significant cause of mortality in Osler-Weber-Rendu disease. For this reason, additional heritable conditions, such as certain of the connective tissue disorders (14), should be considered in early childhood when an intracranial hemorrhage is found at autopsy.

In the current case death was attributed to epilepsy associated with multifocal areas of gliosis and intracerebral vascular malformations. Support for this diagnosis derived from the history of documented grand mal seizures which had developed in the final year of life, epileptogenic foci detected on electroencephalographic testing, and the absence of other lethal disease. Epileptic episodes may also be more common during, or around, the time of menstruation. Although the level of carbemazepine was elevated, it was not within the lethal range and there had been no manifestations of carbemazepine toxicity such as impaired alertness, nystagmus, or tachycardia detected at regular clinical follow-up. The elevated level was due to a recent prescribed increase in dosage because of continued fitting.

Finally, the psychological significance of a major chronic disease should not be underestimated. It is well recognized that adolescents and young adults in particular often do not cope well with chronic illness, resulting in denial of disease and poor compliance with treatment (15). However, although there was evidence in the reported case of considerable stress and depression arising from the disease and associated epilepsy, problems with medication were not thought to be involved in the fatal episode.

Meticulous search for evidence of hemorrhage within the lungs, intestinal tract, and brain should be undertaken at autopsy in known cases of Osler-Weber-Rendu disease. Conversely, if a vascular malformation with significant hemorrhage is found unexpectedly at autopsy, the possibility of Osler-Weber-Rendu disease should be considered. The nasal cavity, mouth, and skin surfaces should be carefully inspected for lesions, the gastrointestinal tract opened in its entirety, and the organs (particularly the lungs and liver) thinly sectioned. Formal neuropathological assessment of the fixed brain in addition to the spinal cord is also advisable. It is also important to determine at autopsy whether the fatal episode has resulted from inappropriate self-medicating or intentional self-poisoning, and to exclude other coincidental causes of natural and unnatural death.

Given the likelihood of an inherited disorder, it is also appropriate at autopsy in suspected cases to sample sterile skin for fibroblast cultures and subsequent molecular evaluation. The heritable nature of the condition makes accuracy of diagnosis even more important, and family screening should be recommended once a diagnosis has been established. This is particularly important if potentially affected female family members are considering pregnancy.

Acknowledgments

We would like to thank the South Australian State Coroner, Mr. Wayne Chivell, for permission to publish details of this case and Prof. Peter Blumbergs, neuropathologist, for his assistance.

References

1. Guttmacher AE, Marchuk DA, White RI. Hereditary hemorrhagic telangiectasia. N Engl J Med 1995;333:918–24.
2. Shovlin CL, Letarte M. Hereditary haemorrhagic telangiectasia and pulmonary arteriovenous malformations: issues in clinical management and review of pathogenic mechanisms. Thorax 1999;54:714–29.

3. Haitjema T, Westerman CJ, Overtoom TT, Timmer R, Disch F, Mauser H, et al. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease): new insights in pathogenesis, complications, and treatment. Arch Intern Med 1996;156:714–9.
4. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 5th Ed. Foster City, CA: Chemical Toxicology Institute, 2000;126–9.
5. Sharma VK, Howden CW. Gastrointestinal and hepatic manifestations of hereditary hemorrhagic telangiectasia. Dig Dis 1998;16:169–74.
6. Kjeldsen AD, Vase P, Green A. Hereditary haemorrhagic telangiectasia: a population-based study of prevelance and mortality in Danish patients. J Int Med 1999;245:31–9.
7. Shovlin CL. Molecular defects in rare bleeding disorders: hereditary haemorrhagic telangiectasia. Thromb Haemost 1997;78:145–50.
8. Osler W. The principles and practice of medicine. London: Butterworth & Co, 1918;613.
9. Mandzia JL, terBrugge KG, Faughnan ME, Hyland RH. Spinal cord arteriovenous malformations in two patients with hereditary hemorrhagic telangiectasia. Child's Nerv Syst 1999;15:80–3.
10. Weik C, Greiner L. The liver in hereditary hemorrhagic telangiectasia (Weber-Rendu-Osler disease). Scand J Gastroenterol 1999;34:1241–6.
11. Robbins SL, Cotran RS, Kumar V. Eds. Pathologic Basis of Disease, 3rd Ed. Philadelphia: WB Saunders Co, 1984;542.
12. Reyes-Mujica M, Lopez-Corella E, Perez-Fernandez L, Cuevas-Schacht F, Carillo-Farga J. Osler-Weber-Rendu disease in an infant. Hum Pathol 1988;19:1243–6.
13. Byard RW, Bourne AJ, Hanieh A. Sudden and unexpected death due to hemorrhage from occult central nervous system lesions. Pediatr Neurosurg 1991–92;17:88–94.
14. Byard RW, Keeley FW, Smith CR. Type IV Ehlers-Danlos syndrome presenting as sudden infant death. Am J Clin Pathol 1990;93: 579–82.
15. Champ CS, Byard RW. Sudden death in asthma in childhood. Forensic Sci Int 1994;66:117–27.

Additional information and reprint requests:
Roger W. Byard
Forensic Science Centre
21 Divett Place
Adelaide 5000, Australia