REVIEW ARTICLE

CURRENT CONCEPTS

HEREDITARY HEMORRHAGIC TELANGIECTASIA

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IDENTIFIED nearly a century ago, hereditary hemorrhagic telangiectasia, or Rendu–Osler–Weber syndrome, has long been viewed as a rare condition producing minor discomfort for affected persons. However, this disorder is now considered to be more common than previously thought,[1-5] and the associated brain and pulmonary lesions are sources of substantial morbidity and mortality.[3,6-8] Wider recognition of the condition and awareness of its sequelae can help avoid the considerable risks associated with its mismanagement. Advances in molecular genetics have demonstrated that hereditary hemorrhagic telangiectasia is actually a group of autosomal dominant disorders.[9-13] The recent identification of the gene causing one form of the condition[14] should lead to a better understanding of these, and perhaps other, vascular disorders.

Although reports as early as Sutton's[15] in 1864 appear to describe what is now known as hereditary hemorrhagic telangiectasia, Rendu[16] first recognized the combination of hereditary epistaxis and telangiectases in 1896 as a specific entity distinct from hemophilia. The following decade produced a number of case reports, including the prominent ones by Osler[17] and Weber,[18] whose names appear in various orders in the common eponymous labels for this condition. In 1909, Hanes[19] coined the term "hereditary hemorrhagic telangiectasia," in acknowledgement of the three features that by then defined the disorder.

Hereditary hemorrhagic telangiectasia occurs with a wide geographic distribution among many ethnic and racial groups. Studies of prevalence show that, at least in the populations investigated, it is more frequent than was formerly thought. It has been found to occur in at least the following numbers: 1 in 2351 members of the population in the French department of Ain,[1] 1 in 3500 on the Danish island of Funen,[2] 1 in 5155 in the Leeward Islands,[4] 1 in 16,500 in Vermont,[5] and 1 in 39,216 in northern England.[3]

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PATHOPHYSIOLOGIC FEATURES

The recognized manifestations of hereditary hemorrhagic telangiectasia are all due to abnormalities of vascular structure (Fig. 1). The smallest of the hallmark telangiectases are focal dilatations of postcapillary venules, with prominent stress fibers in pericytes along the luminal border. In fully developed telangiectases, the venules are markedly dilated and convoluted, extend through the entire dermis, have excessive layers of smooth muscle without elastic fibers, and often connect directly to dilated arterioles. Mononuclear cells, primarily lymphocytes, collect in the perivascular space throughout this process.[20]

Telangiectases are nearly universal, but the other prominent lesions of hereditary hemorrhagic telangiectasia, arteriovenous malformations, appear to be frequent only in certain forms of the condition.[10-12] These malformations, like telangiectases, lack capillaries and consist of direct connections between arteries and veins, but are much larger.

The recent discovery that a gene causing hereditary hemorrhagic telangiectasia encodes a protein that binds transforming growth factor β may help elucidate the basic mechanisms underlying the vascular lesions in the disorder.[14]

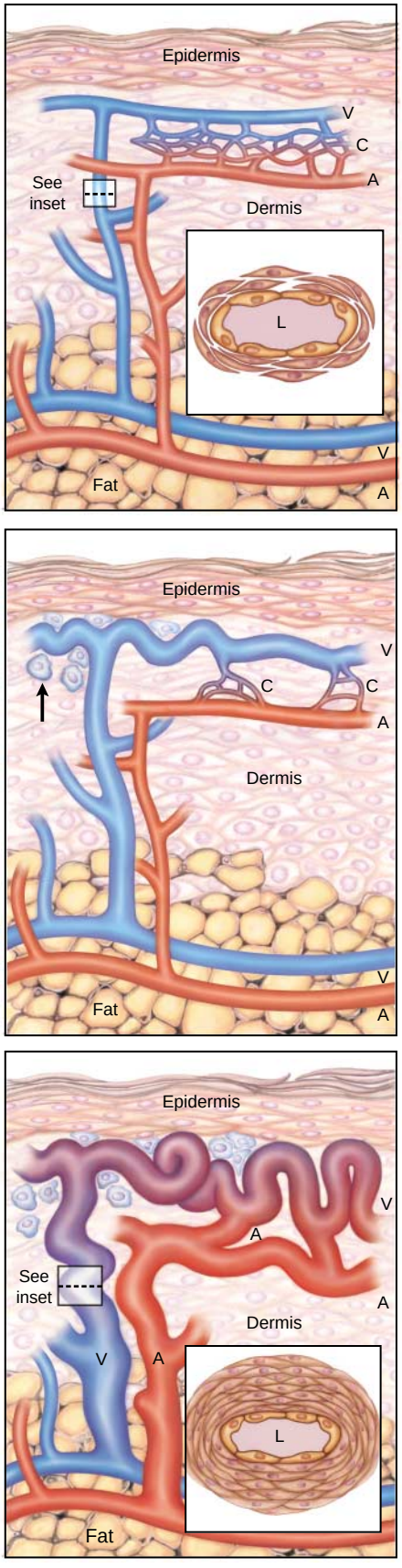
CLINICAL MANIFESTATIONS

The diverse manifestations of hereditary hemorrhagic telangiectasia involve vascular abnormalities of the nose, skin, lung, brain, and gastrointestinal tract. Table 1 summarizes clinical approaches and treatment options in the care of persons with hereditary hemorrhagic telangiectasia.

Nose

Epistaxis caused by spontaneous bleeding from telangiectases of the nasal mucosa is the most common manifestation of hereditary hemorrhagic telangiectasia, occurring in the vast majority of affected persons, but not in all.[21] It may be so severe as to require multiple transfusions and oral iron supplementation, or so mild that hereditary hemorrhagic telangiectasia is never suspected. Recurrent epistaxis begins by the age of 10 years in many patients and by the age of 21 in most,[21] becoming more severe in later decades in about two thirds of affected persons.[21,22]

Multiple treatments for epistaxis have been used, including cauterization, septal dermatoplasty,[23] laser ablation,[24,25] estrogen therapy,[22,26] and transcatheter embolotherapy of arteries leading to the nasal mucosa.[27] Few prospective, randomized clinical trials have evalu-



ated these therapies. One prospective study suggests that estrogen supplementation is ineffective,[26] but larger, uncontrolled studies support its efficacy.[22] Otolaryngologists adept at septal dermoplasty have had good results in patients with severe epistaxis,[23] and laser ablation has been effective in treating milder forms.[24,25]

Skin

Telangiectases of the skin typically present later in life than epistaxis.[6] By the age of 40, most affected persons have multiple telangiectases of the lips, tongue (Fig. 2A), palate, fingers, face, conjunctivas (Fig. 2B),[28] trunk, arms, nail beds, or a combination of these. There may be bleeding from cutaneous telangiectases, but it is rarely clinically important. For telangiectases causing cosmetic concern, topical agents may be useful, and laser ablation can sometimes be effective.[29]

Lung

Pulmonary arteriovenous malformations consist of direct connections between a branch of a pulmonary artery and a pulmonary vein through a thin-walled aneurysm. They are often multiple and appear in both lungs, with a predilection for the lower lobes. It is estimated that 60 percent of persons with pulmonary arteriovenous malformations have hereditary hemorrhagic telangiectasia.[30] Conversely, it is estimated that overall, 5 to 15 percent of persons with hereditary hemorrhagic telangiectasia have pulmonary arteriovenous malformations,[30] but the incidence of these lesions apparently varies according to the specific gene for the condition that is present.[10-12]

Pulmonary arteriovenous malformations result in direct right-to-left shunts and, particularly when multiple, may produce profound dyspnea, fatigue, cyanosis, or polycythemia. Often, however, their initial manifestations are the neurologic sequelae of brain abscess and stroke due to shunting.[31]

Although standard chest radiographs may demon-

Figure 1. Evolution of a Cutaneous Telangiectasis in Hereditary Hemorrhagic Telangiectasia.

In normal skin (top panel), arterioles (A) in the papillary dermis are connected to venules (V) through multiple capillaries (C). These vessels arise from larger arterioles and venules at the junction of the dermis and fat. The ultrastructure of a normal postcapillary venule (shown in cross section in the inset) includes the lumen (L), endothelial cells, and two to three layers of surrounding pericytes. In the earliest stage of cutaneous telangiectasia (middle panel), a single venule becomes dilated, but it is still connected to an arteriole through one or more capillaries. A perivascular lymphocytic infiltrate is apparent (arrow). In a fully developed cutaneous telangiectasis (bottom panel), the venule and its branches have become markedly dilated, elongated, and convoluted throughout the dermis. The connecting arterioles have also become dilated and communicate directly with the venules without intervening capillaries. The perivascular infiltrate is still present. The thickened wall of the dilated descending limb (shown in cross section in the inset) contains as many as 11 layers of smooth-muscle cells. (Adapted from Braverman et al.[20])

strate a typical mass with enlarged arteries and veins, many pulmonary arteriovenous malformations are subtle and appear below the diaphragm because of their posterior location in the lung (Fig. 3). High-resolution helical computed tomographic scanning without the use of contrast material effectively demonstrates the architecture of vessels in pulmonary arteriovenous malformations and has simplified the diagnosis of these lesions.[32] Chest radiography, arterial-blood gas measurements, and finger oximetry remain important in screening persons with suspected pulmonary arteriovenous malformations. Pulmonary angiography is required in order to plan treatments by interventional radiology or surgery.[31,33]

Surgical management of pulmonary arteriovenous malformations has evolved from lobectomy to wedge resection to ligation of the arterial supply of the malformation.[34] Transcatheter embolotherapy with detachable balloons or stainless-steel coils has also been used to close such malformations.[31,33,35,36] Although no prospective studies have compared these approaches, embolotherapy is less invasive than surgery and does not require bilateral thoracotomy to treat multiple malformations. Small remaining malformations may become enlarged after either embolotherapy or surgery. Long-term follow-up of treated patients is important, because the growth of malformations in the interval may require further therapy.

Brain

Neurologic symptoms, including migraine headache, brain abscess, transient ischemic attack, stroke, seizure, and intracerebral and subarachnoid hemorrhage, are common in patients with hereditary hemorrhagic telangiectasia,[8,37] particularly those with a personal or family history of pulmonary arteriovenous malformations.[3,31,38-40] For two thirds of those in whom neurologic symptoms develop, pulmonary arteriovenous malformations are the source of the symptoms.[31] In the remaining third, cerebral or spinal arteriovenous malformations cause subarachnoid hemorrhage, seizure, or less commonly, paraparesis.[4,8,37]

Brain abscess, transient ischemic attack, and ischemic stroke occur exclusively in patients with pulmonary arteriovenous malformations who have right-to-left shunting that facilitates the passage of septic and bland emboli into the cerebral circulation.[31] These symptoms are often the first manifestations of a pulmonary arteriovenous malformation and even of hereditary hemorrhagic telangiectasia itself.[38,40]

The frequency and architecture of cerebral arteriovenous malformations have not been characterized in any large cohort with hereditary hemorrhagic telangiectasia. In one series, 5 percent of patients with hereditary hemorrhagic telangiectasia who underwent computed tomography had cerebral arteriovenous malformations,[31] but the application of more sensitive techniques of magnetic resonance imaging and angiography will apparently demonstrate a higher prevalence.[41]

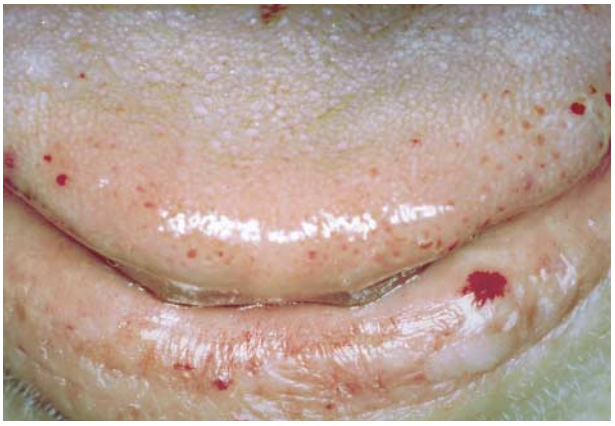
Neurovascular surgery, embolotherapy, and stereotactic radiosurgery have all been used to treat cerebral arteriovenous malformations. Further experience is needed for any single treatment to be recommended as optimal for vascular malformations of the brain or spinal cord in persons with hereditary hemorrhagic telangiectasia.

Gastrointestinal Tract

Recurrent hemorrhage of the upper or lower gastrointestinal tract occurs in a substantial minority of persons with hereditary hemorrhagic telangiectasia[2,42] and is one of the manifestations of the condition that is

Table 1. Summary of Clinical Approaches and Therapeutic Options in Patients with Hereditary Hemorrhagic Telangiectasia.

Affected Organ or System	Type of Lesion	Sites	Symptoms and Signs	Screening Tools	Diagnostic Methods	Appropriate Treatment
Nose	Telangiectases	Nasal mucosa	Epistaxis	Medical history	Visual inspection	Humidification, packing, transfusion, estrogen therapy, septal dermoplasty, laser, cautery, embolotherapy
Skin	Telangiectases	Lips, tongue, palate, face, conjunctivas, trunk, nail beds, finger pads	Bleeding (usually minor)	Visual inspection	Visual inspection	Topical agents, laser ablation
Lung	Arteriovenous malformations	Often multiple; predilection for lower lobes	Cyanosis, clubbing, bruit, migraine, cerebral abscess, embolic stroke	Medical and family history, linkage to 9q3, blood gas measurement, oximetry, chest radiography	High-resolution helical computed tomography, angiography	Embolotherapy, surgical resection, ligation of arterial supply
Central nervous system	Arteriovenous malformations	Brain, spinal cord	Headache, subarachnoid hemorrhage	Medical and family history	Magnetic resonance imaging, magnetic resonance angiography	Neurovascular surgery, embolotherapy, stereotactic radiosurgery
Gastrointestinal tract	Arteriovenous malformations, telangiectases, angiodysplasias	Stomach, duodenum, small bowel, colon, liver	Bleeding; if hepatic lesion, heart failure with bruit	Medical and family history	Endoscopy, angiography; for liver lesions, computed tomography	Transfusion, photocoagulation, estrogen–progesterone therapy



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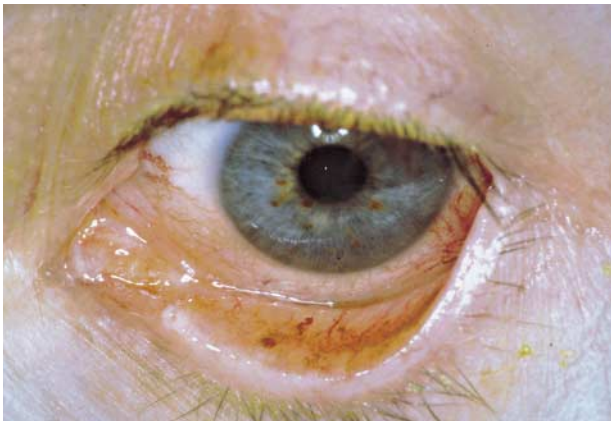

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Figure 2. Telangiectases in Patients with Hereditary Hemorrhagic Telangiectasia.

Panel A shows telangiectases of the tongue and lower lip, and Panel B shows conjunctival telangiectases.

most difficult to manage. Gastrointestinal bleeding does not usually start until the fifth or sixth decade. Endoscopy may reveal telangiectases in the stomach, duodenum, small bowel, or colon that are similar in size and appearance to those of the nasal and oral mucosa. Less commonly, gastrointestinal angiography demonstrates larger telangiectases, arteriovenous malformations, or angiodysplasias.[43] Requirements for the transfusion of more than 100 units of blood are well documented.[44]

Photocoagulation using bipolar electrocoagulation or laser techniques may control bleeding gastrointestinal telangiectases in the short term, but less commonly in the long term.[45,46] A prospective, double-blind, crossover study showed that, as compared with placebo, a mixture of estrogen and progesterone significantly decreased the short-term requirement for transfusion in subjects with hereditary hemorrhagic telangiectasia and gastrointestinal bleeding.[44] The mechanism responsible for the decrease was not determined.

Liver involvement due to the presence of multiple arteriovenous malformations or atypical cirrhosis is a rare but important manifestation of hereditary hemorrhagic telangiectasia.[47,48] High cardiac output caused by left-to-right shunting within the liver can lead to heart failure.[48] Treatment that includes segmental embolotherapy of branch hepatic arteries may be helpful but can produce severe complications.[48]

Molecular Genetics

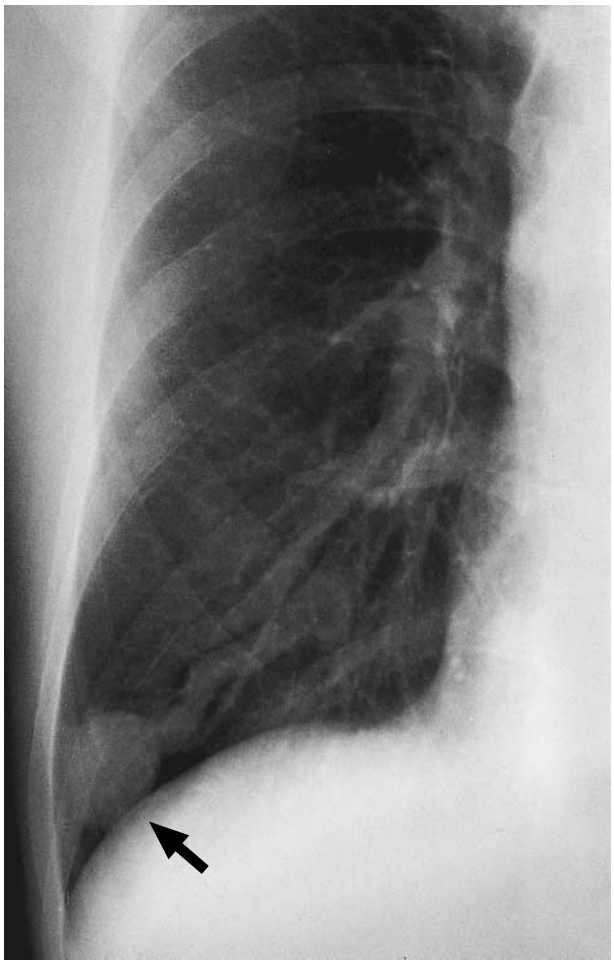
Genetic linkages to hereditary hemorrhagic telangiectasia have been established to chromosome 9q33-q34 in some families[9,49] and to chromosome 12q in others.[13,50] It is possible that genes on other chromosomes may also create the condition.

The gene for hereditary hemorrhagic telangiectasia at chromosome 9q3 has been identified as endoglin,[14] which encodes an integral membrane glycoprotein that is the most abundant protein on endothelial cells to bind transforming growth factor β. This locus appears to initiate a response to the growth factor.[51,52] The mutations of the endoglin gene identified thus far in hereditary hemorrhagic telangiectasia[14] (and unpublished data), including numerous protein truncations, suggest that the altered gene either may produce less of the normal protein ("loss of function" mutations) or may produce a dysfunctional protein that interferes with the remaining normal protein ("dominant negative" mutations). Transforming growth factor β modulates several processes of endothelial cells, including migration, proliferation, and adhesion and the composition and organization of the extracellular matrix. Perturbation of one or more of these processes may cause the vascular dysplasia. The restriction of vascular disease to discrete lesions suggests that an initiation event, mechanical, physiologic, or genetic, is required for the development of each lesion.

Diagnosis

The clinical criterion for the diagnosis of hereditary hemorrhagic telangiectasia is the presence of any two of the following: recurrent epistaxis, telangiectases elsewhere than in the nasal mucosa, evidence of autosomal dominant inheritance, and visceral involvement.[6]

By definition, autosomal dominant diseases are those in which the disease is found in heterozygotes. However, hereditary hemorrhagic telangiectasia shares with many autosomal dominant disorders the property of incomplete penetrance; occasionally, persons who inherit the gene for the disease do not demonstrate it phenotypically. Also, epistaxis, the most common manifestation of hereditary hemorrhagic telangiectasia, is common in the general population. Thus, clinical criteria are not entirely reliable for making the diagnosis, especially in children. The fact that mutations causing hereditary hemorrhagic telangiectasia have been identified raises the possibility of molecular diagnosis. However, preliminary results suggest that many families with disease linked to chromosome 9q3 have unique mutations of the endoglin gene (unpublished data). In other families the gene or genes have yet to be identified. Therefore, DNA-based diagnostics may prove dif-



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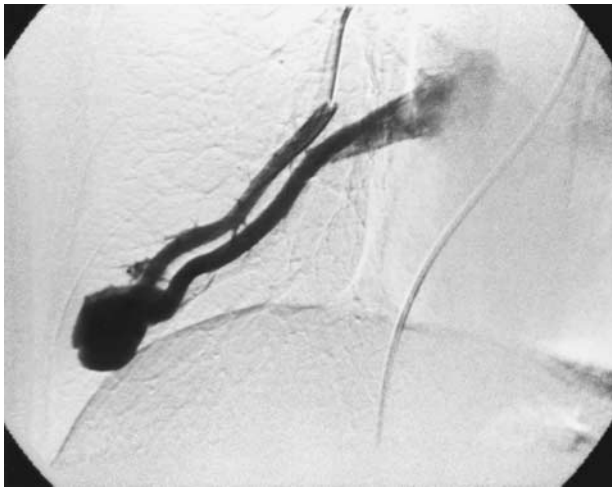

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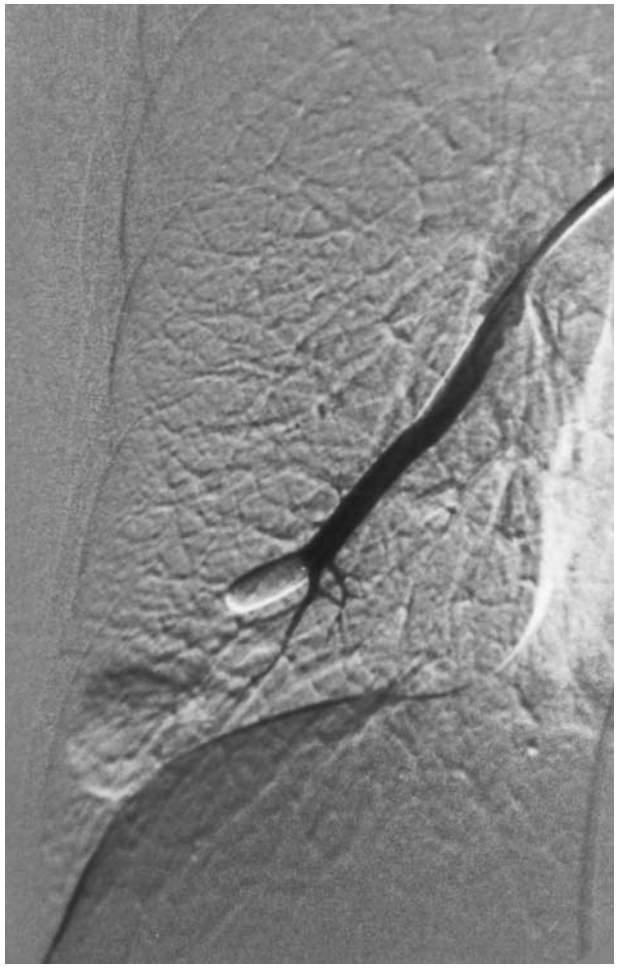

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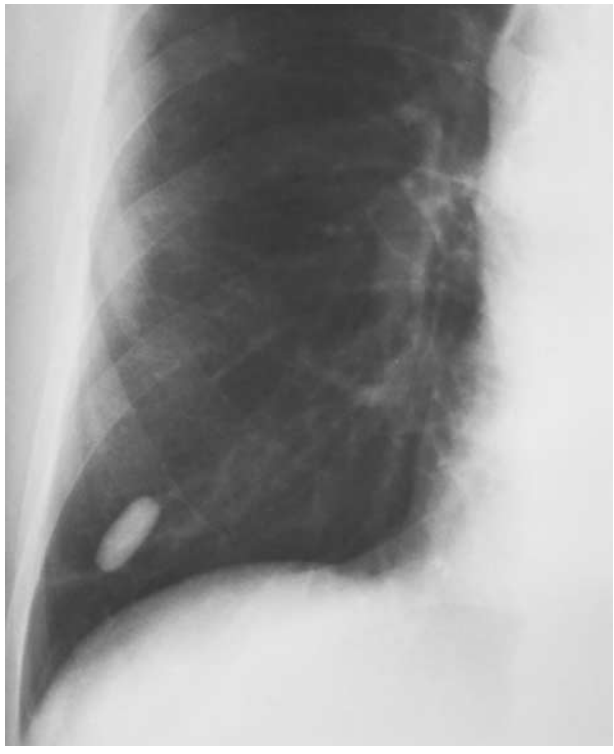

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Figure 3. Treatment of a Pulmonary Arteriovenous Malformation by Embolotherapy.

In Panel A, a chest radiograph shows a pulmonary arteriovenous malformation in the right lower lobe (arrow). Panel B shows a pulmonary angiogram of the same lesion before occlusion. There is an aneurysm with an enlarged artery and vein. Panel C shows the lesion immediately after embolotherapy with a detachable balloon. Panel D shows a chest radiograph of the lesion 30 months after occlusion, with the balloon in place. The aneurysm has disappeared.

ficult, except in research settings or when genetic linkage can be established in a multigenerational pedigree.

Management

Until appropriate studies validate treatment protocols, the care of patients with hereditary hemorrhagic telangiectasia must be based on clinical experience and an understanding of the pathophysiologic features of the disorder. In the follow-up of affected persons, the lung and brain are of particular concern, because each may contain clinically silent lesions that can result in sudden morbidity or death. Presymptomatic intervention in such cases may substantially affect the outcome.

Pulmonary screening attempts to identify persons whose risk of pulmonary arteriovenous malformations is sufficient for diagnostic imaging to be warranted. Measurement of blood oxygen and the family history may both help determine this risk. Because most pulmonary arteriovenous malformations occur near the bases of the lungs, the greatest deoxygenation often occurs when a person is standing (i.e., orthodeoxia), since the gravitational redistribution of pulmonary blood flow increases the flow through basilar malformations. Thus, arterial-blood gas measurements and finger oximetry may be most sensitive when the patient is in the upright position.[31,36] Family history is also important, because molecular evidence of genetic heterogeneity appears to confirm the clinical impression that the incidence of pulmonary arteriovenous malformations varies among families, being particularly high in those with genetic linkage of the condition to chromosome 9q3.[7,10-12]

Persons affected by, or at risk for, hereditary hemorrhagic telangiectasia who have a family history of pulmonary or cerebral arteriovenous malformations should undergo pulmonary screening at puberty, or sooner if the family history includes prepubertal arteriovenous malformations, and again at the end of adolescence. For persons from families without such a history, pulmonary screening should be considered but is less clearly indicated. Because there have been cases of life-threatening pulmonary hemorrhage in the third trimester of pregnancy, affected women should have pulmonary screening before conception.[7] Anyone in whom a pulmonary arteriovenous malformation is found should undergo helical computed tomography every five years to rule out the possible growth of residual malformations in the intervening period.

Family history may also serve as a guide to screening for cerebral arteriovenous malformations and aneurysms, because at least the malformations appear to be significantly more common in certain families. Cerebral screening by magnetic resonance imaging should be performed at least once, preferably in childhood, if there is a family history of cerebral arteriovenous malformations. Even persons at low risk for such malformations are at high risk for cerebral abscess and stroke if they have a pulmonary arteriovenous malformation.

Anyone who has had a pulmonary arteriovenous malformation should receive antibacterial prophylaxis at the time of a dental or surgical procedure. Others who are affected or at risk and who have a family history of pulmonary arteriovenous malformations should use prophylaxis until the possibility that they may have such a malformation is ruled out.

It is important that persons with hereditary hemorrhagic telangiectasia be aware of their diagnosis and its implications and that they inform health care providers that they are affected. Educational materials for patients and providers are available from the HHT Foundation International (P.O. Box 8087, New Haven, CT 06530; 800-448-6389).

Future Developments

The understanding of hereditary hemorrhagic telangiectasia is expanding rapidly. Recently, the condition has been shown to be a family of disorders caused by mutations in various genes, and the gene responsible for one form has been identified. This discovery of genetic heterogeneity should bring a reevaluation of the natural history of these disorders, because the incidence of many clinical manifestations may vary widely among the various forms. A current multicenter effort is attempting to produce the needed correlations between genotype and phenotype. Multicenter cooperation may also lead to randomized, prospective trials to determine the efficacy of various therapies. The development of a functional assay to provide presymptomatic diagnosis appears possible. The finding that a protein binding transforming growth factor β has a key role in the disease should help elucidate the pathophysiologic features. Therapeutic advances, including gene replacement, may now be a realistic possibility given the ease of access through the bloodstream to endothelial cells, the target tissue.

Better understanding of hereditary hemorrhagic telangiectasia may also bring critical insights into other diseases involving vascular damage and repair. Perhaps Osler's hope will be fulfilled: "To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease — these are our ambitions."[53]

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