

Short Report

Sudden death caused by pulmonary thromboembolism in Proteus syndrome

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We report 3 patients with Proteus syndrome (PS) who died suddenly from pulmonary embolism (PE). The first patient was a male diagnosed with PS at 12 years who had varicose veins, portal vein thrombosis, right iliac vein occlusion and recurrent PE. At age 25 years, he was admitted to the hospital with a severe headache. Despite therapeutic doses of warfarin, investigations for an acute episode of breathlessness showed PE and he was unable to be resuscitated. The second case was a 9-year-old male with PS who collapsed at home and could not be revived. Autopsy revealed that the cause of death was a PE associated with thrombosis of the deep veins (DVT). The third patient was a 17-year-old female undergoing inpatient treatment for sinusitis when she unexpectedly arrested. She could not be revived and a full autopsy revealed a large PE with no identified DVT.

We conclude that PE is a serious complication of PS and recommend vigilance concerning the signs and symptoms of thrombosis and PE in individuals with PS, including children. Aggressive evaluation and treatment should be considered urgently in patients with PS and signs or symptoms of DVT.

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Proteus syndrome (PS) is a highly variable disorder whose main clinical findings comprise connective tissue and epidermal nevi, disproportionate overgrowth, early growth of specific tumor types, dysregulation of adipose tissue and vascular malformations (1). No biochemical, cytogenetic or molecular basis for PS has so far been identified. It has been suggested that the condition is caused by a somatic mutation lethal in the non-mosaic state (2). We present 3 patients with PS who suffered fatal pulmonary emboli (PE), a complication not previously recognized to be common in PS.

Case reports

The first patient was a 25-year-old male diagnosed with PS at 12 years because of cerebriiform hypertrophy of the soles, cutaneous nevi, asymmetric right-sided overgrowth and macrodactyly. He developed a severe kyphoscoliosis by age 25 years. Varicose veins were noted in both lower limbs at 16 years. He had portal vein thrombosis with re-

canalization of the portal venous system after warfarin therapy at 19 years of age. He also suffered right iliac vein occlusion with recurrent PE whilst on aspirin at age 24 years. Procoagulant studies without warfarin therapy showed normal levels of protein C, protein S and anti lupus antibody. For one year prior to his last illness, he had persistent, severe headaches that were unresponsive to therapy and for which no underlying cause could be identified. Intracranial hemorrhage was excluded. At 25 years of age, he was admitted to hospital with an unrelenting headache. On day 8 of his admission, he developed tachycardia and hypoxia despite therapeutic doses of warfarin. Investigations showed recurrent PE and he was unable to be resuscitated from an acute episode of breathlessness. A post mortem examination was not performed.

The second case was a 9-year-old male diagnosed with PS because of connective tissue and cutaneous nevi, hemimegalencephaly, asymmetric, progressive overgrowth and bony hyperostoses.

His mother retrospectively recalled that he had complained of leg pain 2 weeks prior to his final illness. He complained of shortness of breath on the day of his arrest and was later found to be unresponsive by his mother. Resuscitation was unsuccessful. At autopsy, pulmonary examination showed pleural effusions and multiple blood clots in the secondary and tertiary branches of the pulmonary arteries. Microscopy of the lungs showed evidence of pulmonary fibrosis and organization of a previous embolus. The PE was thought to have originated from deep vein thromboses in both legs and relative immobility due to PS was considered to be a predisposing factor. Other abnormalities found at postmortem and ascribed to PS were cerebriform hypertrophy of the right palm and plantar hyperplasia of the soles, linear epidermal nevi of the right neck, chest and abdomen, macrodactyly, asymmetric overgrowth of the right side and widespread bony exostoses and deformities with severe lordosis of the spine and contractures of multiple joints. There were multiple internal vascular malformations. Examination of the brain showed absence of the septum pellucidum and there was a right porencephalic cyst with reduced white matter in the right periventricular region.

The third patient was an 18-year-old female who had soft tissue hypertrophy of the soles, hemihypertrophy, macrocephaly and kyphoscoliosis consistent with PS. She had been undergoing inpatient treatment for sinusitis and refractory otitis media when she unexpectedly arrested and could not be revived. Autopsy revealed an extensive embolus at the bifurcation of the main pulmonary artery and non-occlusive thrombi in the veins of the left popliteal fossa.

Discussion

PS is rare and the natural history of the condition has not been clearly delineated. There are few case reports describing adults with the condition and this could be explained by premature mortality or biased ascertainment. Sudden death is an important aspect of the history of PS. Joseph Merrick (a.k.a. 'The Elephant Man') died unexpectedly at 29 years of age in April 1890, while in residence at the London Hospital. The cause of death was attributed to asphyxia (3), although no autopsy records have been found.

Sudden death in PS also occurred in a 5-year-old child who had apneic episodes and possible seizures but an autopsy did not indicate significant pulmonary findings (4). Other causes of death in PS have included restrictive lung disease and pneumonitis (5), pneumonia complicated by respiratory

failure secondary to rib overgrowth (6), laryngospasm (3), cerebellar abscesses (3), and sepsis with cerebral abscesses and bronchopneumonia (7).

PE have not been included among the pulmonary manifestations of PS. The most frequently reported pulmonary abnormalities in PS are cystiform anomalies involving the pleura and associated with severe emphysema, atelectasis, and fibrosis (8, 9). A bronchial hamartoma resulting in aspiration pneumonitis (5) and a diffuse increase in interstitial lung markings have also been noted (10).

To our knowledge, PE have previously been described in only 2 patients with PS (11, 12). The first patient was an 11-year-old female diagnosed with PS because of right hemihyperplasia, anisomelia, right plantar hyperplasia, kyphoscoliosis and digital exostoses (11). Two days following a second surgical procedure for progressive kyphosis, she suffered a cardiac arrest and was unable to be resuscitated. Autopsy showed emboli in the right pulmonary arteries and a haemorrhagic infarct of the right lung (11). The second patient was a 2-year-old male undergoing surgical convalescence who had asymmetric overgrowth, macrodactyly and widespread internal lymphaticovenous malformations (12). The source of the emboli was presumed to be the pelvic veins or the lower extremities (12).

It has been hypothesized that large vascular lesions can increase the risk of thromboemboli following the report of a 4-week-old infant with an extensive hemangioma of the left knee and consumption coagulopathy who died suddenly during treatment (13). It therefore becomes important to consider the extent and severity of the vascular malformations in PS, which may predispose patients to PE.

Vascular anomalies have been considered to be a common feature of PS (6, 8, 14–16) and were present in 38/55 (69%) of cases in one report (17). Abnormalities have included prominent, enlarged and or dilated veins over the chest, spine, abdomen and lower limbs (6, 18–20). Prominence of the superficial veins may be particularly marked over areas of significant hypertrophy and is enhanced by atrophy of the underlying subcutaneous tissues (21, 22). Conversely, absence of the right superficial femoral vein (23) and absence of the left saphenous vein have been reported (20).

Varicose veins are also common in PS (3, 5, 6, 13, 20, 24) and can be present from several months of age (25). The varicosities occur independently of limb overgrowth (26) and can affect the upper limbs (27). Other vascular malformations have in-

cluded vascular nevi (3, 6) and cavernous hemangiomas (3, 22, 26). Cutis marmorata (27) and capillary malformation of the skin have also been documented (23, 27, 28).

In contrast, abnormalities affecting the deep venous system have rarely been reported in PS. Numerous markedly dilated thrombosed veins were found in the submucosa of the sigmoid colon, rectum and urinary bladder in one patient at autopsy (3). Another patient with a philtral port-wine stain, asymmetry, macrodactyly, macrocephaly and an epidermal nevus had recurrent thromboses of the left iliac vein (28). Probable thrombophlebitis involving a thigh tumor has also been described (24).

Thrombophlebitis and thromboembolism may be more common in Klippel–Trenaunay syndrome (KTS; OMIM 149000), a condition that has clinical overlap with PS but that can be clearly differentiated from PS. KTS is characterized by atypical varicosities, anomalies of the deep venous system (atresia, hypoplasia, valvular incompetence and aneurysmal dilatation) and vascular nevi (29–33). The incidence of thrombophlebitis has ranged from 12.5% (32) to 53% (32) and the incidence of thromboembolism from 11% (33) to 22% in KTS patients (30).

PE have been described in large studies and in individual case reports of patients with KTS (30, 32–36). One study found that 6/49 (12%) of patients had had at least one PE (30) and concluded that the tenfold-increased risk of postoperative thromboembolism in adults with KTS necessitated preoperative antithrombotic prophylaxis (30). The severity of the PE in KTS can be judged from other reports in which a 53-year-old man with recurrent PE died despite anticoagulation (34) and a 21-year-old woman continued to have embolic episodes after insertion of a filter into the inferior vena cava (35).

DVT and PE have not been reported in several other syndromes distinguishable from but having clinical overlap with PS, including Bannayan–Zonana syndrome (37), Sturge–Weber syndrome (38) and encephalocraniocutaneous lipomatosis (39).

We would therefore recommend vigilance regarding the development of deep venous thrombosis or PE in patients with PS who have widespread or internal vascular lesions and/or patients who undergo surgery. Cases with clinical overlap with KTS may be at particular risk for the development of thromboembolism and PE arising from abnormalities of the deep venous system. The emboli in KTS have been thought to be associated with vascular malformations and a corresponding consumptive coagulopathy or with an abnormality of

fibrinolysis (29). However, a prothrombotic tendency has not yet been excluded in these patients.

Conclusions

We conclude that PE are a serious complication of PS and that they may contribute to the apparently elevated mortality in PS. We recommend that pediatricians and surgeons consider aggressive evaluation and treatment in patients with PS and signs or symptoms of DVT and/or PE. Appropriate prophylaxis for patients immobilized for surgery should also be considered.

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