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PAPER

PATHOLOGY/BIOLOGY

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Lower Extremity Deep Venous Thrombosis with Fatal Pulmonary Thromboembolism Caused by Benign Pelvic Space-Occupying Lesions—An Overview

ABSTRACT: Venous stasis predisposes to thrombosis. One hundred and sixty cases of fatal pulmonary thromboembolism were reviewed to determine how many cases had deep venous thromboses associated with venous blood flow reduction caused by external pressure from benign pelvic masses. Three cases were identified, representing 2% of cases overall (3/160): a 44-year-old woman with a large uterine leiomyoma (1048 g); a 74-year-old man with prostatomegaly and bladder distension (containing 1 L of urine); and a 70-year-old man with prostatomegaly and bladder distension (containing 3 L of urine). Although a rare cause of fatal deep venous thrombosis and pulmonary thromboembolism, space-occupying pelvic lesions can lead to extrinsic pressure on adjacent veins reducing blood flow and causing stasis and thrombosis. Individuals with large pelvic masses may, therefore, be at increased risk of pulmonary thromboembolism from deep venous thrombosis, particularly in the presence of concurrent risk factors such as immobility, thrombophilias, malignancy, and significant cardiopulmonary disease.

KEYWORDS: deep venous thrombosis, forensic science, leiomyoma, pelvic mass, prostatomegaly, pulmonary thromboembolism venous stasis

Blood coagulates when there are alterations to vessel wall integrity, blood flow, or blood components (1,2). Risk factors for deep venous thrombosis therefore include local factors such as limb immobilization, and more general factors such as malignancy and recent surgery (1,3). Increasingly, the potential role of intrinsic hypercoagulable states is also being recognized (2,4). While altered coagulation status may not be provable at autopsy, a number of other risk factors may be identified. It is routine for pathologists to try to identify the source of a thromboembolus at autopsy and also to check for any predisposing factors. The present study was undertaken to determine how frequently reduction in iliac venous return owing to benign local pelvic pathology was encountered as a cause of deep venous thrombosis leading to fatal pulmonary thromboembolism in a group of individuals presenting with sudden and unexpected death. The range of possible pelvic lesions that may cause such obstruction was also reviewed.

Materials and Methods

One hundred and sixty cases where sudden and unexpected death had been attributed to pulmonary thromboembolism were randomly selected from the case files of Forensic Science SA, Adelaide, South Australia, from January 2004 to December 2008. Case files were reviewed and cases were selected where pulmonary thromboembolism had been attributed to deep venous thrombosis associated with reduction in pelvic venous blood flow because of external pressure from a local pelvic mass. Case details including age, gender, underlying medical conditions, and autopsy findings were summarized. The findings in the legs were limited to documentation of deep venous thrombosis as the leg circumference and presence or absence of pitting edema were not always documented. Forensic Science SA is the South Australian state forensic facility where medico-legal autopsies are performed. The population served is approximately 1.6 million. All of the cases had undergone full autopsies with complete coronial and police investigations.

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Results

A total of three cases of lethal pulmonary thromboembolism were identified where there had been venous compression from a benign pelvic space-occupying lesion. This represented 2% of cases overall (3/160).

Case 1

A 44-year-old woman with no significant past medical history collapsed suddenly and subsequently died. At autopsy, the main pathological findings were deep venous thrombosis of the left calf with pulmonary saddle thromboembolism and bilateral peripheral pulmonary thromboemboli. In addition, a large uterine leiomyoma weighing 1048 g was found occupying the pelvis with compression of pelvic veins. Death was caused by pulmonary thromboembolism secondary to deep venous thrombosis of the calf. No other predisposing factors to deep vein thrombosis were found.

Case 2

A 74-year-old man who had a past history of "skin cancer" was found deceased at his home address. At autopsy, the main pathological findings were deep venous thrombosis of the right calf with bilateral pulmonary thromboemboli. In addition, there was prostatomegaly with trabeculation of the bladder wall in keeping with long-standing obstruction of urinary outflow. The bladder was distended by 1 L of urine and was compressing the pelvic veins. Other findings of note included cardiomegaly with septal scarring of the left ventricle and a squamous cell carcinoma of the left cheek. Death was caused by pulmonary thromboembolism secondary to deep venous thrombosis of the calf. No other predisposing factors to deep venous thrombosis were identified (the squamous carcinoma of the face was not locally infiltrating or metastasizing and so was considered incidental).

Case 3

A 70-year-old man with a past history of recurrent falls, schizophrenia, atrial fibrillation, aortic stenosis, and type 2 diabetes mellitus died while he was in hospital following a fall. At autopsy, deep venous thrombosis of the right calf was present with bilateral pulmonary thromboembolism. In addition, there was prostatomegaly with trabeculation of the bladder wall in keeping with long-standing obstruction of urinary outflow. The bladder was distended by 3 L of urine and was compressing the pelvic veins. Other findings of note included cardiomegaly, severe coronary atheroma, and old cerebral infarction. Death was caused by pulmonary thromboembolism resulting from deep venous thrombosis of the calf. Another predisposing factor to deep venous thrombosis in this case included immobility.

A 50-year-old woman was also identified whose sudden death was attributed to pulmonary thromboembolism who had a massive (12.65 kg) benign ovarian tumor. This case was not included in the study as the tumor occupied much of the abdominal cavity, not just the pelvis, with evidence of inferior vena caval obstruction.

Discussion

Pulmonary thromboembolism is responsible for a significant number of deaths each year in Western countries (1). The incidence and survival rate of pulmonary thromboembolism have not changed markedly in recent years, remaining stable despite advances in prophylaxis, imaging, and treatment (1). The pathogenesis of venous thrombosis has traditionally been explained by abnormalities in the three components of Virchow's triad: (i) blood stasis, (ii) endothelial injury, and (iii) hypercoagulability (4). Therefore, those most at risk of deep venous thrombosis and subsequent pulmonary thromboembolism are those with abnormalities in one or more of these three components, all of which should be carefully checked for at autopsy. Risk factors are similar at all ages although pulmonary thromboembolism is uncommon in the very young (5,6).

Immobility resulting in blood stasis is a common and well-recognized risk factor for deep venous thrombosis and pulmonary thromboembolism (1,3). The most important causes of immobility include recent surgery with general anesthesia, a past history of stroke with extremity paralysis, long-haul travel, and hospitalization for significant illness (1–4,7,8). Quadriplegia and paraplegia are also significant causes of immobilization, and so, patients with spinal cord injuries are at increased risk (1,7). Limb immobilization also imparts significant risk of thrombus formation with postoperative orthopedic patients having an increased rate of deep venous thrombosis and subsequent pulmonary thromboembolism (2,4,7). Less commonly, pulmonary thromboembolism may arise from the periprostatic venous plexus (9). The present study has focused specifically on the potential role that local pelvic factors may have in a forensic population in causing venous stasis from external compression of veins that drain the lower limb.

Causes of hypercoagulable states are diverse and include both inherited and acquired conditions. Inherited thrombophilias increase the likelihood of any thrombotic event, important examples of which include factor V Leiden (a point mutation in the factor V gene leading to activated protein C resistance) as well as protein C and protein S deficiencies (1,2,4,7). Acquired hypercoagulable states can also be caused by disseminated malignancy, antiphospholipid antibody syndrome, and sepsis (1,2,4,10). An important cause of antiphospholipid antibody syndrome is lupus anticoagulant (2,11). Oral contraceptive pill use, hormone replacement therapy, and pregnancy may also be associated with hypercoagulable states (1,2,4,7). Hyperhomocysteinemia has been associated with a mild increase in the risk of venous thromboembolism. Hyperhomocysteinemia can be inherited or acquired (2,12).

Endothelial damage is less important than stasis and hypercoagulability in the pathogenesis of venous thromboembolism (2) and is most commonly caused by trauma or recent surgery to the lower limb (1,4).

In addition to these three traditional causative factors, general debility and reduced cardiopulmonary reserve confer both an increased risk of pulmonary thromboembolism and an increased risk of right ventricular decompensation and resultant mortality (1). Reduced cardiopulmonary reserve is associated with several conditions including congestive cardiac failure, chronic obstructive pulmonary disease, interstitial lung disease, ischemic heart disease, and significant cardiomegaly. The risk of deep venous thrombosis and pulmonary thromboembolism also increase exponentially with age (3,4,13,14), most likely due to decreasing mobility, the presence of multiple comorbidities, and increasing systemic activation of coagulation pathways (2,4). Furthermore, the risk of pulmonary thromboembolism may also be greater in overweight individuals, possibly mediated by the hypercoagulable state of obesity (15,16). Given the aging and increasingly overweight/obese population of many Western countries, pulmonary thromboembolism may, therefore, be more often encountered in forensic morgues as a cause of sudden death.

In the current study, three cases were found where it was considered that simple external mechanical pressure on veins by a pelvic mass had contributed to lower limb venous stasis with subsequent thrombosis. In one case, a large uterine fibroid had compressed veins and in the remaining two, reduced venous blood flow was attributed to the effects of enlarged bladders. Two of the cases had other risk factors such as cardiovascular disease and immobility. As these cases represented only 2% of the total number of individuals with fatal pulmonary thromboembolism over the time course of the study, pelvic venous compression by a benign space-occupying lesion appeared to be an uncommon predisposing factor to thrombosis. The cases also demonstrated that for a pelvic mass to cause significant mechanical obstruction to local venous blood flow, it must be of considerable size. However, given the high incidence of both uterine leiomyomas and bladder outflow obstruction in older individuals, it may be that these conditions should be monitored more closely in individuals with other risk factors for venous thrombosis. Had regular catheterization been undertaken in case 3, venous obstruction may not have occurred.

In turning to the literature, a range of benign pelvic space-occupying lesions have caused lower limb venous stasis. These cases

are, however, uncommon, resulting in mainly lower extremity edema or deep venous thrombosis, with only a small number of cases leading to embolic sequelae.

Uterine leiomyomas are the most common pelvic tumors in women, occurring in 20–30% of women over 30 years of age. Despite the frequency of uterine leiomyomas, cases of associated deep venous thrombosis and pulmonary thromboembolism are uncommon (17,18). The mechanism by which a large leiomyoma may cause venous stasis and subsequent thrombosis in pelvic and lower limb vessels is thought to be simple extrinsic mechanical compression of veins by the tumor, rather than the effects of estrogen or hypercoagulable states (17–22). Other benign uterine and ovarian tumors have also caused extrinsic mechanical compression of pelvic veins, leading to obstruction of venous flow and subsequent thrombosis (23).

Pelvic venous obstruction as a result of a massively distended bladder has been previously reported (24–29). In most of these cases, bladder distention was secondary to benign prostatic hypertrophy and bladder outlet obstruction, although rare cases have been reported secondary to neurogenic bladder (28,29). In all cases, the mechanism of thrombosis was thought to be secondary to pelvic venous stasis from extrinsic compression by the distended bladder (24,25,27). Significant pressure on the pelvic veins has been demonstrated clinically when the bladder volume exceeds 300 mL of urine (27). The clinical presentations of these cases were varied, ranging from simple lower limb edema to massive pulmonary thromboembolism.

Pregnancy is a well-recognized risk factor for deep venous thrombosis and pulmonary thromboembolism, with a prevalence of 0.1–0.2% (30–33). Although the underlying mechanisms are multifactorial, involving a hypercoagulable state, endothelial injury, and stasis, hypercoagulability is most important (31). The hypercoagulable state of pregnancy is thought to be a protective measure to prevent peripartum maternal hemorrhage, which is still a major cause of maternal death in the developing world (31,32). The hypercoagulable state is brought about by activated protein C resistance and reduced protein S anticoagulant activity, in addition to raised blood levels of fibrinogen, von Willebrand factor, and factors VII, VIII, IX, and X (16,31). Endothelial injury is most important in the postpartum period as there can be vessel trauma during both vaginal and operative delivery (16). Stasis may be caused by a combination of progesterone-mediated venodilation and extrinsic obstruction of pelvic vessels by the gravid uterus (16,30,31). However, although mechanical compression of pelvic veins by the gravid uterus may play a role in deep venous thrombosis during pregnancy, it is not the major factor.

Less common causes of venous stasis because of external pressure have involved psoas abscesses that can be primary or secondary (34,35). Primary psoas abscesses are in themselves relatively rare but may cause iliac vein compression (34). Pelvic venous obstruction has also been reported by a psoas abscess secondary to sigmoid diverticulitis (36). The mechanism of deep venous thrombosis associated with psoas abscess is thought to involve a combination of endothelial injury as a result of leukocyte migration causing endothelial desquamation and subsequent exposure of subendothelial collagen, and venous stasis because of mechanical compression (34,36).

Pelvic venous obstruction secondary to mechanical compression by a large synovial cyst of the hip has been reported, with venous stasis of lower limb vessels manifested clinically as lower limb edema without thrombosis (37). A case of cyclic compression of the external iliac vein secondary to extraperitoneal endometriosis has also been described (38). Finally, several cases of pelvic venous flow obstruction secondary to mechanical compression by penile prosthesis reservoirs have occurred because of malpositioning of the reservoirs (39–41).

TABLE 1—*Causes of external compression of pelvic veins resulting in lower limb venous stasis.*

Tumors	Uterine and Ovarian Tumors
Distended bladder	Benign prostatic hypertrophy
	Neurogenic bladder
Soft tissue masses	Psoas abscess
Miscellaneous	Gravid uterus
	Synovial cyst
	Endometriosis
	Penile prosthetic reservoir

This study and literature review have demonstrated that although benign pelvic masses may cause mechanical obstruction of adjacent veins (Table 1), this phenomenon is a rare cause of fatal and nonfatal pulmonary thromboembolism. The low rate of embolic sequelae may be due to the fact that mechanical compression and obstruction of pelvic veins may also physically impede embolization of thrombus material.

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