Plenary lectures

Venous thrombosis: the history of knowledge

P.M. Mannucci

Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Maggiore Hospital and University of Milan, Italy

Key Words

Venous thrombosis, thrombophilia

Abstract

Venous thrombosis is a frequent disease. It is surprising, therefore, that no case truly compatible with a diagnosis of venous thrombosis was apparently reported in the antiquity. There is no case that could be reasonably attributed to a venous thrombus in the writings of Hippocrates, Galenus, Celius Aurelianus, Ibn an-Nafiz, Avicenna and others. Venous thrombosis is not among the many diseases mentioned in the Bible. The term "leucophlegmasia", first used by Hippocrates and then by Celius Aurelianus, refers to cases of bilateral leg edema, most likely due to conditions such as heart failure, liver cirrhosis and renal insufficiency. Nothing compatible with a diagnosis of venous thrombosis can be found in pieces of art from ancient Egypt, Greece, Rome, Persia and South America. While in these sources there are sometimes representations of varicose veins and ulcers, unilateral leg edema or other pictures compatible with venous thrombosis are not featured. The first well documented case of venous thrombosis is depicted in a beautifully illustrated manuscript written in the 13th century and currently preserved in

Paris at the Bibliothèque Nationale (MS Fr 2829, Folio 87). The manuscript describes the case of a young man from Normandy named Raoul who at the age of twenty developed unilateral edema in the right ankle that subsequently extended up to the thigh, with no obvious symptoms in the contralateral leg. Raoul was advised to visit the tomb of Saint Louis who was buried in the church of Saint Denis, where the patient spent several days confessing his sins and praying the saint. Afterwards he chose to collect the dust accumulating below the stone that covered the tomb and to apply it on the fistulae and ulcers of his foot. The openings stopped running and were filled with flesh. He was first obliged to use crutches but subsequently he could walk with a cane, to be eventually able to dispose of all devices, even though his foot throbbed a little. Raoul was cured as described above in the year 1271 and was still alive and well in 1282. Not only this is the first case of venous thrombosis, the young age of the patients leads us to suspect that Raoul had a thrombophilic condition.

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Prof. P.M. Mannucci
Via Pace 9
20122 Milano – Italy
Tel. +39/02/55035421
Fax +39/02/50320723
e-mail: piermannuccio.mannucci@unimi.it and/or pmmannucci@libero.it

Introduction

No case truly compatible with a diagnosis of venous thrombosis was apparently reported in antiquity. Extensive search by medicine historians found no case that could be reasonably attributed to a venous thrombus in the writings of Hippocrates, Galenus, Celsus Aurelianus, Ibn an-Nafiz, Avicenna and others [1-4]. Venous thrombosis is not among the many diseases mentioned in the Bible [5]. The term “leucophlegmasia”, first used by Hippocrates and then by Celsus Aurelianus, refers to cases of bilateral leg edema, most likely due to conditions such as heart failure, liver cirrhosis and renal insufficiency. Nothing compatible with a diagnosis of venous thrombosis can be found in pieces of art from ancient Egypt, Greece, Rome, Persia and South America. While in these sources there are sometimes representations of varicose veins and ulcers, unilateral leg edema or other conditions compatible with venous thrombosis are not featured. Particularly surprising is the absence in antiquity of descriptions of venous thrombosis during pregnancy and in the post-partum period, because it is difficult to imagine how unilateral swelling of a leg accompanied by signs of inflammation could have escaped the attention of the concerned team attending labour (the midwife, the mother and other relatives of the pregnant woman).

According to Dexter and Folch Pi [6], the first well documented case of venous thrombosis is depicted in an illustrated manuscript written in the 13th century and currently preserved in Paris at the Bibliothèque Nationale (MS Fr 2829, Folio 87). The manuscript describes the case of a young man from Normandy named Raoul who at the age of twenty developed unilateral edema in the right ankle that subsequently extended up to the thigh, with no obvious symptoms in the contralateral leg. The case illustrated in the manuscript is reported in more detail in an essay by Guillome de Saint Pathus on the miracles of Saint Louis (Louis IX), included in a collection of *Fay* [7] of *Classiques Français de Moyen Age*. From the description it is clear that during the course of his illness the young man developed a septic leg with ulcers and fistulae and that the great and much renowned surgeon, Henri du Perche, advised him to wait and see. This conservative attitude at a time when surgery was the main approach to illnesses indicates that what is now common knowledge was already understood, i.e., that in the treatment of venous thrombosis there is little space for surgical intervention. The subsequent course of the illness was characterized by further deterioration, with exposure of bone from the ulcers and fistulae and clear manifestations of gangrene. Raoul was advised to visit the tomb of Saint Louis who was buried in the church of Saint Denis, where the patient spent several days confessing his sins and praying the saint. Afterwards he chose to collect the dust accumulating below the stone that covered the tomb and to apply it on the fistulae and ulcers of his foot. The openings stopped running and were filled with flesh. He was first obliged to use crutches but sub-

sequently he could walk with a cane, to be eventually able to dispose of all devices, even though his foot throbbed a little. Raoul was cured as described above in the year 1271 and was still alive and well in 1282. Not only this appears to be the first case of venous thrombosis, the young age of the patients and the absence of circumstantial risk factor leads us to suspect that Raoul had a thrombophilic condition.

Pathogenesis

Risk factors. It is now well established that venous thrombosis is caused by a contribution of three factors, i.e., damage to the vein wall, blood stasis and hypercoagulability. It is also known that thrombosis is more frequent in association with circumstantial risk factors such as pregnancy and delivery, surgery, cancer and other medical illnesses; and with inherited and acquired factors that cause hypercoagulability. The development of our current knowledge on the pathogenesis of venous thrombosis took place over several centuries.

The first detailed description of venous thrombosis after delivery was made in England in 1676 by Richard Wiseman, Sergeant-Chirurgion to King Charles II. In a chapter of *Several Chirurgical Treatises* [8] he wrote about the wife of a pharmacist who, after a difficult labour, developed swelling and pain of the right leg, extending from the knee to the hip, with no inflammation and discolouring of the skin. The description by Wiseman of this case is notable not only because the concept of the proximal propagation of a leg venous thrombus is put forward, but also because Wiseman surmised that thrombus formation was due to systemic alteration in circulating blood, thereby pioneering the concept of hypercoagulability. Until the end of the 18th century, it was held that venous thrombosis associated with pregnancy and delivery was due to retention in the legs of “evil humors”, which determined a reflux of blood. For instance, the famous French surgeon Ambroise Paré who lived in the 16th century believed that swelling of the legs during pregnancy was due to the retention and concentration of menstrual blood. Incidentally, Ambroise Paré was probably the first to describe superficial thrombophlebitis as a complication of varicose veins, as he wrote: “They often swell with congealed and dried blood”.

Another widely held view was that post-partum thrombosis was due to the retention of unconsumed milk in the legs (“engorgements laiteux”). The short but well documented and detailed publication of Findley [9] should be read by those who are interested in one of the earlier modern reviews on venous thrombosis associated with childbirth.

With the exception of the first case of venous thrombosis in the apparently healthy young man described by Guillome de Saint Pathus, the early descriptions of this condition were mostly related to childbirth. We have to wait until the 19th cen-

tury and the seminal work of Armand Trousseau¹⁰ to have the first documented case of the association of venous thrombosis with cancer, known to be one of the most frequent predisposing conditions. His observation had to wait nearly 70 years to be confirmed and extended by Sproul [11], who reported a high frequency of venous thrombosis during the post-mortem examination of patients who died of various malignancies, most notably carcinoma of the pancreas. According to De Bakey [12], a pioneer in cardiovascular surgery who in 1954 reviewed the early literature, the association between venous thrombosis and surgery was first recognized by Spencer Wells in 1866. More modern, seminal studies are those of Gunnar Bauer [13] who in 1942 called attention to the frequency of venous thrombosis, especially after fractures of the legs; and of Byrne [14] who in 1955 investigated as many as 748 cases and demonstrated that the post-operative state was the second most common predisposing factor (pregnancy and puerperium ranking first), particularly in cancer surgery, in operations involving the pelvis and in fractures of the legs. That medical illnesses, particularly if long-lasting and associated with prolonged immobilization in bed, are a risk factors for venous thrombosis was first established in 1810 by Ferrier [15], who noted that the condition occurred not only post-partum but also during debilitating infectious diseases such as typhus. According to Lockwood [16], however, it was as early as at the beginning of the 15th century that Ugo Benzi of Siena described venous thrombosis occurring during a long illness accompanied by fever in a man from Novara named Jacobus Manni. Swelling involved both legs, so that it is not sure that conditions other than venous thrombosis may have caused it.

The Virchow triad. In 1628 William Harvey demonstrated for the first time the circulation of the blood in "De Motu Cordis". Hunter [17] and his disciples Matthew Baillie [18] and William Hewson [19] abandoned the theory of retention of humors and hypothesized that venous thrombosis was due to closure of the veins by blood clots. They thought that slowing of the circulation of the blood was a prominent pathogenic mechanism and that thrombus formation was due to the presence of a "coagulable lymph" in plasma, a substance later called fibrinogen. In the year 1800 Hull [1] wrote the first review of the literature on venous thrombosis that he called for the first time "phlegmasia dolens" and hypothesized that coagulation of the "lymph" was due to inflammation. A seminal step forward towards understanding the pathophysiology of venous thrombosis was made in the second half of the 19th century through the seminal work of Rokitsky [20] and particularly of Virchow [21]. On the basis of pathological observations mainly made in fatal cases of post-partum thrombosis they independently proposed the famous triad of factors that are still considered the main factors in the pathogenesis of venous thrombosis, i.e., damage to the vein wall, slowing of venous flow and changes in the blood leading to an increased tendency to form clots (hypercoagulability).

In post-partum phlegmasia dolens, the epitome of venous thrombosis at that time, damage to the vein was related to manipulation of the uterine veins where thrombosis was thought to begin; stasis, due to confinement in bed and to the process of parturition itself; hypercoagulability, from vaginal bleeding that as early as in 1604 has been observed to increase blood coagulability (Roderiguez a Castro, cited by Anning [2]). However, the biochemical and molecular basis of the third component of the Virchow triad, hypercoagulability, remained only partially understood until recently. It has been known for a long time that in situations associated with an increased risk of venous thrombosis (pregnancy and the puerperium, estrogen use, the post-operative state and cancer) there is an acquired increase in the plasma concentration of a number of coagulation factors (particularly factor VIII and fibrinogen), often accompanied by an impairment of a defensive system such as fibrinolysis. However, it was only in 1965 that the existence of genetic factors increasing the risk of venous thrombosis through the induction of hypercoagulability was given a biochemical basis Egeberg [22] reported that in a Norwegian family characterized by venous thrombosis occurring at a young age and with a tendency to recur there was reduction of antithrombin to half-normal levels and that this defect was closely linked with the thrombotic tendency. This finding appeared immediately biologically plausible, because antithrombin is a naturally occurring anticoagulant protein which inactivates the main coagulation enzymes (thrombin, activated factor X, activated factor IX and activated factor XI). Antithrombin deficiency, however, explained only a small proportion of cases of venous thrombosis, being present in as few as 0.1 % or less of patients with a first episode of this disease. A step forward was made in the early 1980s, when the American groups of investigators led by John Griffin [23] and Charles Esmon [24] independently showed that protein C and protein S deficiencies were inherited risk factors for venous thrombosis, accounting together for approximately 0.5% of first episodes of the disease [25]. The active enzymatic form of protein C with its cofactor protein S inactivates the activated form of coagulation cofactors V and VIII, making biologically plausible that the deficiency of protein C and protein S lead to decreased inactivation of these coagulation cofactors and ultimately to a hypercoagulable state. Despite these discoveries on the genetic basis of hypercoagulability and of the associated risk of thrombosis, the great majority of cases of venous thrombosis, particularly those occurring in the absence of circumstantial risk factors, remained unexplained. In 1993 Dahlback [26] and his colleagues in Malmo (Sweden) demonstrated in patients with a history of venous thrombosis a relation between the inherited resistance of plasma to the anticoagulant action of activated protein C and the development of venous thrombosis, a finding confirmed in the same year by Griffin et al [27], Koster et al [28], and Faioni et al [29]. On the next year Rogier Bertina [30] and his team in Leiden discov-

ered that the inherited resistance to activated protein C was associated with a missense mutation in the gene encoding coagulation factor V, that dramatically slowed the cleavage of the activated form of this cofactor by activated protein C. The mutation, called factor V Leiden, leads to a gain of function of activated factor V, that in turn causes a hypercoagulable state [31,32]. The striking finding was that activated protein C resistance resulting from heterozygosity for the factor V Leiden mutation is present in approximately 20% of patients who present with a first episode of venous thrombosis [28], and that in populations of European descent the background frequency of the mutation is 2 to 3% or higher. The reasons for the high frequency of the Leiden mutation, that originates from a single founder, are still partially understood but have led to interesting evolutionary hypotheses. Hypercoagulability associated with the mutation might have conferred advantages to men in the "fight or flight" pattern of the primitive life and favoured women by causing less blood loss at the time of parturition. The discovery of activated protein C resistance and of the factor V Leiden mutation has been a fundamental breakthrough in clinical medicine, as witnessed by the fact that pub-

lished papers related to these findings have been quoted more than 2000 times in eight years. After the original description of the factor V mutation, the Leiden group led by Bertina has made a further important contributions by identifying another frequent gain-of-function mutation in another coagulation zymogen, factor II or prothrombin, associated with hypercoagulability and thrombosis [33]. The substitution of one nucleotide in the non-coding region of the gene at 3' leads to an increased potential for the formation of the enzyme thrombin from the zymogen, and to an increased risk of venous thrombosis. Overall, the two forementioned inherited abnormalities associated with hypercoagulability contribute to explain, alone or in association with circumstantial risk factors, approximately 25 to 30% of first, unselected cases of venous thrombosis and 60 to 70 % of cases of recurrent thrombosis and of thrombosis in the young. Among the acquired risk factors associated with hypercoagulability, the antiphospholipid antibody syndrome and particularly the lupus anticoagulant add substantially to the genetic factors in the modern understanding of hypercoagulability. The pioneer of this concept, Robert Wiseman, will smile satisfied in his grave.

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