Review

ARTICLE

DERMATOLOGICAL MANIFESTATIONS OF VENOUS DISEASE. PART II: RETICULATE ERUPTIONS

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Introduction

The reticulate pattern is probably one of the most important dermatological signs that signifies the involvement of the underlying vascular networks and the cutaneous vasculature. It is seen in benign forms of livedo reticularis and in more sinister conditions such as Sneddon's syndrome. There is considerable confusion in the literature with different authors having utilised a variety of terms including livedo reticularis, livedo racemosa, cutis marmorata and retiform purpura when communicating about the same or entirely different conditions. This confusion arises from the historical and geographical origin of these terms. For instance, the term livedo racemosa has a European root and is more widely used in French and German literature. The term livedo is a description of a colour (livid, violet) and not a pattern. The term reticularis refers to the reticulate netlike pattern. However, many physicians wrongly refer to the reticulate pattern as the livedo or livedoid pattern. Finally, a variety of sub classifications of livedo reticularis such as transient, persistent, systemic, idiopathic, blanchable and necrosing have added to the confusion.

This paper reviews the historical evolution of knowledge in this field and presents a simple classification of the conditions involved based on their pathophysiology. The next instalment of this review will examine purpura and thrombohaemorrhagic disorders and the final instalment will be dedicated to vascular anomalies.

ABSTRACT

Cutaneous patterns are often the only clue to a complex underlying vascular pathology. Reticulate pattern is probably one of the most important dermatological signs of venous or arterial pathology involving the cutaneous microvasculature and its presence may be the only sign of an important underlying pathology. Vascular malformations such as cutis marmorata congenita telangiectasia, benign forms of livedo reticularis, and sinister conditions such as Sneddon's syndrome can all present with a reticulate eruption. The literature dealing with this subject is confusing and full of inaccuracies. Terms such as livedo reticularis, livedo racemosa, cutis marmorata and retiform purpura have all been used to describe the same or entirely different conditions. To our knowledge, there are no published systematic reviews of reticulate eruptions in the medical literature.

This article is the second in a series of papers describing the dermatological manifestations of venous disease. Given the wide scope of phlebology and its overlap with many other specialties, this review was divided into multiple instalments. We dedicated this instalment to demystifying the reticulate pattern. The next paper will discuss purpura and thrombohaemorrhagic disorders.
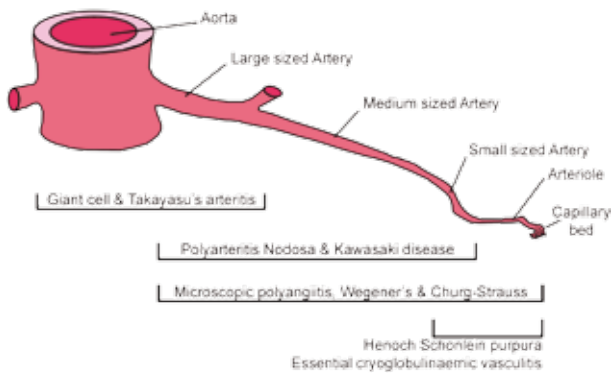
Classification of vessel size

The most widely used classification of vessel size was developed to define and categorise different types of vasculitis (Table 1).[1] This classification divides the vessels into large, medium and small. Large vessel refers to the aorta and its major branches, including the extracranial branches of the carotid artery. Temporal arteritis is hence classified as a large vessel vasculitis. Medium-sized vessel refers to the main visceral arteries such as renal, hepatic, coronary, and mesenteric arteries. Medium-sized arteries of the subcutaneous plexus and reticular veins fall into this category. Small vessel refers to venules, capillaries, and arterioles (Figure 1). Telangiectasias (post-capillary venules) are classified as small.

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Table 1: *Names and classification of vasculitides adopted from the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis.*

Nomenclature of Systemic Vasculitis		
Large vessel vasculitis	**Medium sized vessel vasculitis**	**Small sized vessel vasculitis**
Giant cell arteritis	Polyarteritis nodosa	Wegener's granulomatosis
Takayasu disease	Kawasaki disease	Churg-Strauss syndrome
	Thromboangiitis obliterans	Microscopic polyangiitis
	Mesenteric inflammatory veno-occlusive disease	Henoch-Schönlein purpura
		Essential cryoglobulinemic vasculitis
		Cutaneous leukocytoclastic angiitis

Figure 1: *Vascular tree & its correspondence with vasculitis*

Based on this classification, leukocytoclastic vasculitis is a small vessel vasculitis involving post-capillary venules, whereas Giant cell (Temporal) arteritis is a large vessel vasculitis of the Temporal arteries.

This classification is a useful tool for describing vasculitis but is not consistent and therefore has limited application in phlebology and vascular medicine.

Vascular Networks

The cutaneous, subcutaneous and fascial vasculature is organised into a number of horizontal vascular networks (Figure 2). These include two cutaneous vascular plexi (subpapillary and subdermal), three subcutaneous vascular plexi (superficial, middle and deep) and the fascial plexus. All these networks contribute to the blood supply of the skin.[2]

As blood enters the skin, arterioles repeatedly ramify and then drain into the sheet-like plexi. Ascending arterioles and descending venules are paired as they connect these layers. The plexi are elegantly located at set anatomical boundaries: subpapillary, subdermal, subcutaneous and fascial. Dermal arterial inflow consists of a series of ascending arterioles that rise perpendicularly to the skin surface to form a subpapillary plexus. From the subpapillary plexus, arterial capillaries arise to form the dermal papillary loops that represent the nutritive component of the skin circulation. Each ascending arteriole is situated at the centre of a cone that supplies a set hexagonal area of skin (Figure 3). The capillary beds drain into the subpapillary venous plexus at the periphery of the bed. Blood flows from the arteriole at the centre of the bed to venules at the periphery of the bed.

Occlusion or vasospasm of arteries involving the horizontal vascular layers and in particular the subdermal or subcutaneous plexi will affect large areas of skin, whereas pathology affecting the ascending arteries or arterioles affects only small areas of skin.

Cutaneous Vascular Networks

There is confusion in the literature whether the cutaneous vascular network consists of two or three horizontal plexi. Some authors refer to three plexi, a sub-epidermal plexus just below the rete ridges from which the capillary loops arise, a dermal plexus at the junction of papillary and reticular dermis and a subdermal plexus at the junction of dermis and the subcutaneous tissue.[2-4] Bravermann[3] places the subepidermal plexus at the junction of papillary and reticular dermis and as the equivalent of the 'subpapillary' plexus and hence describes only two cutaneous plexi. Here we follow Bravermann's description.

The Subpapillary Plexus

This plexus lies at the junction of papillary dermis with reticular dermis and is responsible for thermoregulation (Figure 2). Ascending arterioles arising from the subdermal plexus supply the subpapillary plexus. Venules of this plexus

Vascular Networks
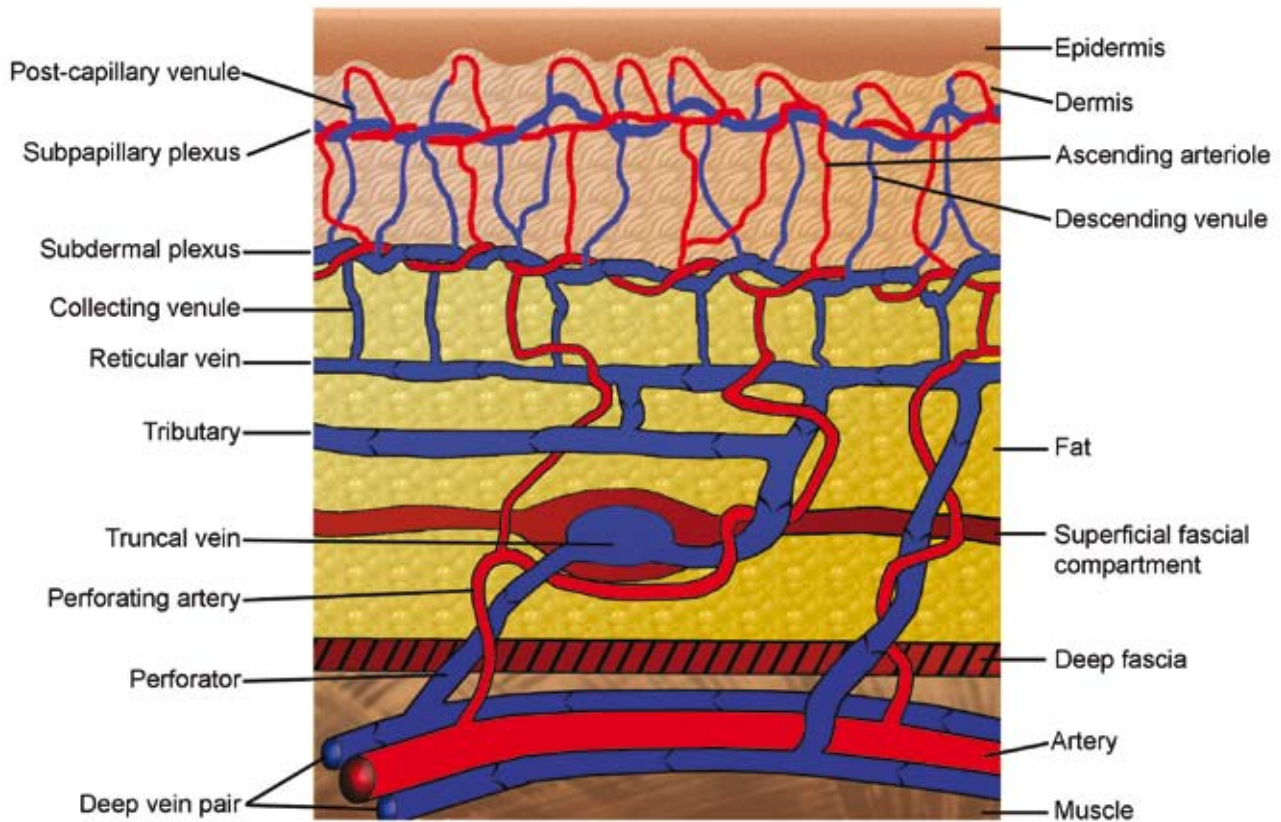

Figure 2: *Vascular Networks*

drain into the subdermal plexus via the descending venules that run perpendicular to the skin surface. Capillary loops arise from this plexus. The arterioles of this plexus are high resistance terminal arterioles. The tips of the capillary loops are located near the dermo-epidermal junction and may be only 100 microns from the epidermal cells that they supply. These are the primary sites for exchange of oxygen and nutrients, and a region characterised by maximal thermal gradient due to its proximity to skin surface.[5] Generally, a single capillary loop extends into one dermal papilla. Highly innervated structures called precapillary sphincters control the flow of blood between the arterioles and capillaries (Figure 4). The precapillary sphincters contain muscle fibres that allow them to contract. When the sphincters are open, blood flows freely to the capillary beds. When the sphincters are closed, blood must flow directly from the arteriole to the venule through arterio-venous anastomoses. As the capillary loops descend towards the subpapillary plexus, they take on the characteristics of the postcapillary venule.[6]

Postcapillary venules form the venous aspect of this plexus and are the site where inflammatory cells migrate from the vascular to the extravascular compartment.[7,8] Dilatation of the postcapillary venules results in clinically evident telangiectasias seen in venous disease. This is also the site most affected by small vessel vasculitis. Postcapillary venules drain into descending venules that run perpendicular to the surface of the skin. Descending venules drain into the subdermal plexus.

The Subdermal Plexus

This plexus is the most significant of the horizontal vascular layers and has a primary role in distribution of blood supply to other regions of skin. The subdermal plexus lies at the junction of dermis and the subcutaneous fat (Figure 2). Arterioles arising from this plexus supply the pilosebaceous and sweat glands. The subdermal veins of the subdermal plexus are called 'collecting veins'. These veins have bicuspid valves oriented to prevent reflux into the dermal vessels. Collecting veins drain into subcutaneous vessels such as the larger reticular veins, venous tributaries or even superficial truncal veins. Collecting veins can even drain straight into deep veins via perforating veins. The subdermal plexus derives its arterial supply from small arteries ascending from the subcutaneous plexus. These small arteries can be visualised ultrasonically in the subcutaneous fat with thick echogenic walls.
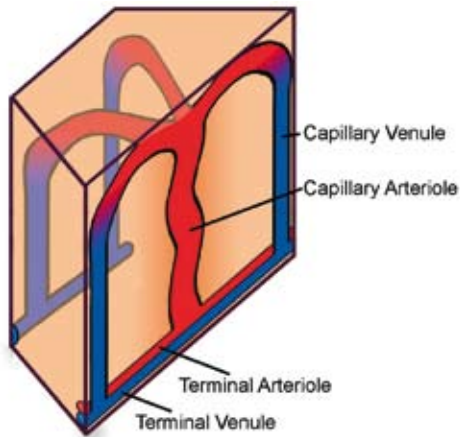
Figure 3: *Basic Hexagonal Arteriolar Unit. This diagram demonstrates the capillary loop & its arteriolar unit. Larger arterial vessels such as ascending arterioles & musculocutaneous arteries form similar but larger hexagons.*

Figure 4: *Arteriovenous (AV) anastomosis and its relationship with the capillary loop*

The Subcutaneous Vascular Network

The subcutaneous tissue contains three vascular plexi: superficial, middle and deep. The cutaneous vascular network receives branches from all three plexi.

The subcutaneous venous network forms a large-capacitance reservoir for venous blood. Sluggish flow in this network leads to the purplish colour seen in venous congestion.

The Fascial Vascular Network

The subcutaneous plexus derives its arterial supply from the fascial plexus. The fascial plexus derives its blood supply from both inter-muscular and intra-muscular arteries.
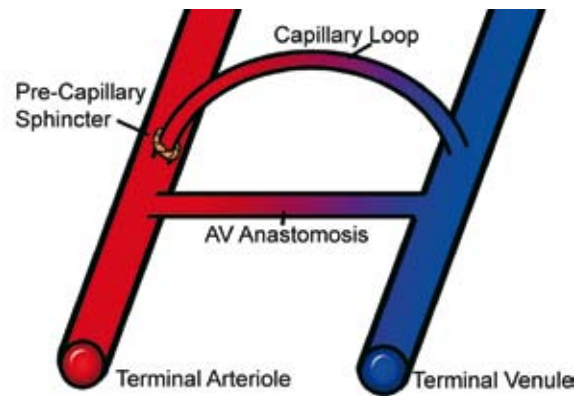
Inter-muscular arteries (Direct Cutaneous Arteries)

These travel within the fascial septae and in between the muscles to pass directly to skin. Examples of such arteries include septocutaneous and fasciocutaneous vessels. These vessels supply blood only to the skin, and not to muscle. They run parallel to the skin surface for much of their course and supply large areas of skin. Intra-arterial injection of these arteries will cause necrosis of large areas of skin (Figure 5).

Intra-muscular Arteries (Musculocutaneous Arteries)

These arise from large, named branches of the aorta and, as the name suggests, pass through the underlying muscles before reaching the skin. These arteries supply blood to both muscle and skin. Musculocutaneous arteries run perpendicular to skin for much of their course, supplying only a small area of skin. Vasospasms of these arteries can induce vasospastic conditions such as Bier's spots

or vasospastic livedo reticularis. Veno-arteriolar reflex vasospasm of these vessels secondary to sclerotherapy or intra-arterial injection of these vessels with sclerosants will cause necrosis of small areas of skin (Figure 6).

Cutaneous Lymphatics

Cutaneous lymphatic channels play an important role in the immune system.[9] Langerhans cells use the cutaneous network of lymphatics to reach their target lymph nodes. Having sampled antigen, the Langerhans cells migrate into lymphatic vessels, passively flow to lymph nodes and present the sample antigens to T-cells. T-cells then use the cutaneous vasculature to get to the site of sampling to deal with the potential threat.

Apart from their function as a transport network for the immune system, lymphatic channels are important in regulating pressure of the interstitial fluid by resorption of fluid released from the vessels and in clearing the tissue of cells, proteins, lipids, bacteria and degraded substances. Fluids and their contents enter the lymphatic system because of the open junctions but remain in the lymphatic system because of the closed ones. External pressure variation is necessary for interstitial fluid uptake and transport.

Lymphatic capillaries

Lymphatic capillaries (also called initial lymphatics or terminal lymphatics) are the first portal of entry into the lymphatic system. These are blind-ending vessels located in the papillary dermis but do not extend as close to the epidermis as capillary loops. The capillary lymphatics drain into a dermal (subpapillary) horizontal plexus just below the dermal venous plexus.

Figure 5: Stellate necrosis and haemorrhagic bulla due to an intra-arteriolar injection of sodium tetradecyl sulphate. Septocutaneous arteries supply larger areas of skin & intra-arterial injection of sclerosants will cause necrosis of large areas.

Figure 6: Stellate necrosis post-sclerotherapy due to veno-arterial reflex (VAR) vasospasm of musculocutaneous arteries supplying the skin. These arteries rise perpendicular to the skin & hence only supply small areas.

Pre-collector lymphatic vessels

Pre-collector lymphatic vessels run perpendicular to the surface of skin and drain the dermal lymphatic plexus into a sub-dermal lymphatic plexus. Some of the pre-collectors act as perforating lymphatics and drain into the deep lymphatic system (perforating pre-collectors). Some pre-collector vessels contain valves.

Lymphatic collectors

Lymphatic collectors are the vessels of the subdermal lymphatic plexus. They run in the superficial fat layer parallel to the skin. The lymphatic collectors receive the lymph from pre-collectors and transfer it into the lymph nodes and the lymphatic trunks. Lymphatic collectors contain bicuspid valves. The segment between the valves is called a lymphangion. Lymphangions have an autonomic contraction of 10-12 contractions per minute at rest. This contraction rate increases as a response to increased lymph formation, external stretch, temperature, muscle contraction and other stimuli.

Regulation of Blood Supply

Thermoregulation

The abundance of cutaneous vessels is more than sufficient to meet the metabolic needs of the skin. The cutaneous vasculature is involved in thermoregulation, blood pressure, wound repair and numerous immunological activities. Thermoregulation is the primary function of the skin's rich circulation and nutrition is only a secondary consideration.

The cutaneous vascular layers play an important role in heat dissipation. The depth of each vascular plexus from the epidermal surface is determined by the thermal equivalence of conduction, convection, and radiation from the body surface. Equally important is the superficial network of reticular veins lying a few millimetres below the skin surface. The rate of blood flow in this plexus can be altered as much as a hundredfold.

Under normothermic conditions, the skin's blood flow is relatively low at about 5% of cardiac output. Under thermal stress, the large surface area of skin provides the ideal mean for dissipation of heat. The supplying arteries are dilated, and the blood flow to skin may reach 8 L/min and up to 60% of the cardiac output.[10] Under cold stress, the arteries that supply the skin are constricted. The blood flow may be reduced to as little as 20 to 50 ml/min to the skin of the entire body.

The neural control of cutaneous vasculature is complex. Central nervous system (CNS) and not the local metabolic control regulates cutaneous blood flow. This is in contrast to local metabolic control for muscle blood flow. Sympathetic noradrenergic nerves cause vasoconstriction, whereas sympathetic cholinergic nerves provide active vasodilatation using acetylcholine and vasoactive intestinal peptide (VIP) as neurotransmitters. Cholinergic sudomotor nerves increase sweating during thermal stress.[10]

Arteriovenous Anastomoses (AVA)

AVAs are direct communications between terminal arterioles and venules without the capillary intervention (Figure 4). The literature dealing with AVAs and their role in thermoregulation often contains contradictory and confusing information.[5, 11, 12]

AVAs have thick muscular walls, heavy noradrenergic sympathetic innervation and lie deep to capillary loops. AVAs are plentiful acrally in the feet, hands, lips, nose, and ears. Some acral AVAs are heavily endowed with glomus cells. These structures are generally innervated by a rich supply of cholinergic nerve fibres.

At normal body temperature, the sympathetic tone keeps these shunts almost totally closed. Under thermal stress, the sympathetic drive from the hypothalamus abates, and active vasodilatation through cholinergic nerves causes maximum vasodilatation of supplying arteries. This way warm blood can bypass the high resistance terminal arterioles and capillary loops and enter directly into the superficial venous plexi via AVAs. By reaching the superficial venous plexus (SVP) the surface area for heat exchange is rapidly increased and more efficient heat dissipation is achieved.

Under cold stress, the sympathetic drive from the hypothalamus will cause vasoconstriction of the supplying arteries, AVAs and capillary loops. Given the increased number of AVAs in acral areas, less blood will get to the ears, hands, feet, nose, and lips. Dermal arterioles in other parts of the body also constrict and limit arterial blood flow into the SVP. Skin blood flow can be virtually abolished under these extreme conditions. Excess stimulation of the sympathetic nervous system through the hypothalamus or adrenal glands in response to cold stress can significantly reduce blood flow to the skin, as with Raynaud's disease. Cold can also induce the precipitation of cryoglobulins and similar proteins, which can present clinically with livedo racemosa or reticulate necrosis.

Advanced venous hypertension can cause permanent opening of the AVAs due to increased venous pressure. Under these conditions, capillary loops appear elongated and tortuous and may look glomerular. Open AVAs redirect arterial flow from capillaries and hence these capillaries are thought to contribute less to nutrition.[13] Open AVAs may also play a role in the development of ulceration post-sclerotherapy.[14, 15]

Veno-arteriolar Reflex (VAR)

A rapid dilatation of the cutaneous veins, such as that caused by obstruction, causes a reflex vasospasm of the supplying arteries to reduce the inflow of blood to the region. This rapid dilatation is interpreted as outflow obstruction and the reflex is designed to prevent further flow into the area where the outflow is obstructed. Sympathetic vasoconstrictor nerves mediate this reflex vasospasm. Rapid injection of a sclerosant into a superficial vein, especially into a previously treated partially sclerosed vein, can trigger this reflex vasospasm. VAR in combination with sludge formation causes occlusion of the affected arteries, which presents with stellate purpura and necrosis of the corresponding skin.

The arterial vasospasm causes blanching of the skin. The blanching is gradually replaced by reactive hyperaemia, which is clinically observed as erythema. Prolonged blanching usually indicates a high probability of ulceration.[16]

Phlegmasia alba dolens, phlegmasia cerula dolens [14] and the Nicolau syndrome probably share a similar underlying pathogenic mechanism.

Reactive Hyperaemia

Reactive hyperaemia is a measure of regional vascular reactivity in response to tissue hypoxia. The increase in regional blood flow after vascular occlusion is directly related to the severity and duration of ischemia.[17] During the period of occlusion, tissue hypoxia and a number of metabolites such as adenosine produced during the hypoxic state dilate arterioles and decrease the vascular resistance. After restoration of the perfusion pressure, the flow is increased because of the reduced vascular resistance. During hyperaemia, oxygen is replenished and vasodilator metabolites are washed out of the tissue, causing the resistance vessels to regain their normal vascular tone and thereby to return the flow to normal levels.

The longer the period of occlusion, the greater the metabolic stimulus for vasodilation, leading to increases in duration of hyperaemia. In general, the ability of an organ to exhibit reactive hyperaemia reflects the autoregulative capacity of its microcirculation.[18] Increased skin microvascular oscillation frequency at rest and in the hyperaemic state after an ischemic stimulus is associated with increased mortality in patients suffering from multiple organ dysfunction.[19]

Reticulate Eruptions

Morphology

Non-Reticulate Formations

Conditions affecting small sized veins present with round macules or papules. For instance, small vessel vasculitis, an inflammatory condition of post-capillary venules will present with small round lesions of palpable purpura (Figure 7). Small vessel pathology involving ascending arterioles can present with hexagonal macules (see below).

Reticulate Formations

A reticulate or net-like eruption is formed of multiple rings (Figure 8). When there is an arterial pathology, each individual ring is centred by a feeding arterial vessel (artery, arteriole or capillary arteriole) that supplies an area of skin in the shape of an arterial hexagon (Figure 9). Obviously, the size of the hexagon will depend on the size of the arterial vessel involved.
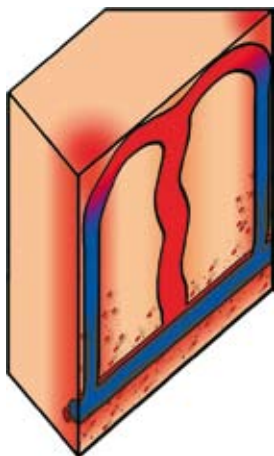
When there is a venous pathology, each individual ring is rimmed by draining venous vessels (vein, venule or capillary venule) forming a venous ring. When there is medium sized

vein pathology, the individual ring is formed by the actual involved superficial veins creating large venous rings (Figure 10). When the pathology involves the capillary or post-capillary venules, smaller venous rings form at the periphery of arterial hexagons (see below) (Figure 9). In general, conditions affecting the central aspect of the ring are arterial in nature, and conditions affecting the rims are venous.

The confluence of a small number of rings form a stellate (star-like) pattern seen clinically with post-sclerotherapy ulceration (Figures 5, 6 and 12). Partial involvement of a number of rings will present in a branched (racemosa) pattern (Figure 13). Involvement of a larger number of rings will form a reticulate pattern (Figure 14), which can be generalised or localised.

Arterial Hexagons

The basic unit of a reticulate arterial eruption is a single hexagon. Each individual ring is formed of a hexagon at the centre of which is a single involved arterial vessel (Figure 9). The hexagon signifies the cutaneous territory supplied by the central arterial vessel. Conditions affecting a single vessel will present with a single hexagonal ring and not in a reticulate
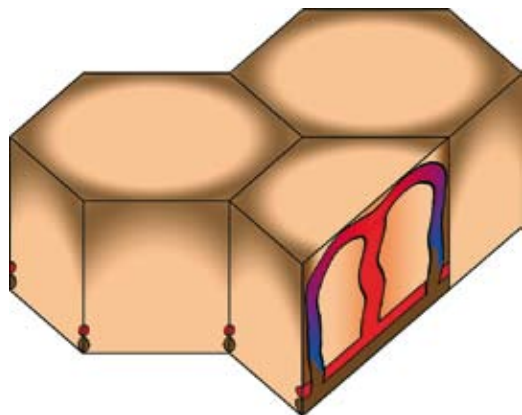
pattern. The size of the individual hexagon is determined by the size of the underlying vessel involved. Larger rings are due to the involvement of the larger and deeper arteries whereas smaller rings signify the involvement of smaller and more superficial vessels. For example, Bier's spots are caused by vasospasm of small musculocutaneous arteries that travel perpendicular to the skin and present with small hexagonal macules (Figures 9 and 15). Infarction of small arteries will cause hexagonal scars of atrophie blanche (Figures 16 and 17). Intra-arterial injection of sclerosants, VAR caused by sclerosants or other causes of obstruction of a single vessel can cause a hexagonal or multi-hexagonal (stellate) necrosis (Figure 5, 6 and 12). Vasospastic livedo reticularis is due to involvement of these cutaneous arterial hexagons, which demonstrate central blanching (Figure 9). Congestion of deoxygenated blood at the rim of these hexagons is due to slow flow in the draining veins secondary to reduced arterial inflow (Figure 18). With arterial hexagons, the centre is abnormal and biopsy should be taken from the centre of the ring.

Venous Rings

Pathological involvement of the reticular veins (Figure 10) of the subcutaneous superficial venous plexus can induce a reticulate eruption (Figure 14). The individual venous rings are different to arterial hexagons as they lack the symmetrical formation. The livid rings of the venocongestive sub-type of livedo reticularis can appear as an exaggeration of the normal venous rings of the subcutaneous reticular venous system (Compare Figure 10 with Figure 14). The rings appear pronounced due to reduced blood flow and lowered oxygen tension in these veins. Blanching of the cyanotic rim may reveal the underlying venous vessel. Thrombosis and purpura affecting these veins can present with larger rings demonstrating pathology along the rims (Figure 19).

Figure 7: *Small vessel vasculitis affecting the post-capillary venules presenting with round palpable purpura. Small red circles present the extravasated red blood cells & black dots represent the inflammatory infiltrate.*
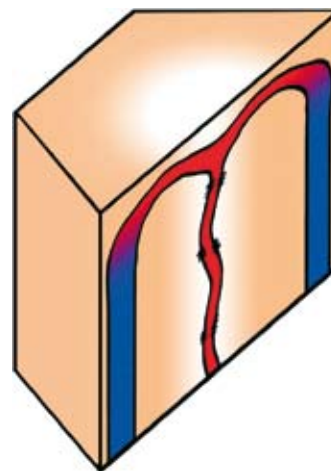

Figure 8: *Venous congestion secondary to outflow obstruction in the absence of an arterial pathology. This may be seen in the venocongestive sub-type of livedo reticularis.*

Figure 9: *Vasospasm of the central arterial vessel generating a blanched appearance in the centre of the arterial hexagon*

Pathology involving capillary or post-capillary venules will create smaller venous rings at the periphery of arterial hexagons (Figures 8 and 11). This can be either due to decreased arterial inflow causing a decreased venous outflow or due to obstruction to the venous outflow. In both situations, venous congestion involves the rims of the arterial hexagons. Blanching of the cyanotic rim in this case does <u>not</u> necessarily reveal an affected vessel due to the small size of the vessel and its orientation to the skin surface which in case of descending venules, is perpendicular to the skin (Figures 8 and 11).

With venous rings, the rims contain the pathology and the central skin is normal. Biopsy should be taken from the periphery of the ring and not the centre.

Stellate Pattern

Involvement of a small number of hexagons will form a stellate pattern. Occlusion of small arteries or arterioles can cause punched out stellate necrosis (Figures 12). Examples include those associated with sclerotherapy or septic embolisation (Figure 6).

Branched Pattern

Localised but partial involvement of a number of rings will present with a segmental branched version of the reticulate pattern. The branched pattern is caused by partial involvement of a number of arterial hexagons or venous rings.

The best clinical example is livedo racemosa (Figure 13). Livedo racemosa is a partially blanchable, branched segmental reticulate eruption. For example, polyarteritis nodosa, an inflammatory vasculitis of medium sized arteries presents with livedo racemosa. The appearance is caused by partial involvement of a number of arterial hexagons.

Reticulate Pattern

The reticulate pattern signifies the involvement of the superficial vascular networks and in particular the larger medium sized vessels of the subcutaneous vascular plexi. Reticulate pattern has been wrongly referred to as livedoid despite the fact that livedo refers to the colour and not the pattern.

Examples of the reticulate pattern include the veno-congestive sub-type of livedo reticularis, which is due to slow flow and congestion of deoxygenated blood in the subcutaneous superficial venous plexus (Figure 14). This sub-type of livedo reticularis presents with a cyanotic (livid), blanchable reticulate eruption. Livedo vasculopathy is due to thrombotic occlusion of medium sized veins. It presents with a non-blanchable reticulate purpura and ultimately pigmentation (Figures 19 and 20).

When the reticulate eruption is generalised, the presentation can be symmetrical and bilateral. Otherwise, a reticulate eruption can be localised or segmental. For example, purpura caused by cholesterol emboli or livedo vasculopathy can be described as localised reticulate purpura (Figure 21).

Historical Perspectives

The most well known reticulate eruption is livedo reticularis. The term livedo is derived from the Latin word lividus meaning pale blue. It was first used by Hebra in 1860 to designate a violet discolouration of the skin due to a "local disturbance of circulation" as opposed to central cyanosis.[20] Hebra also introduced livedo calorica to describe "a bluish colour of skin consequent to the influence of cold" that disappeared on pressure as well as on re-warming of the skin. He found this discolouration similar to the netlike pattern seen on the skin of corpses. Clearly, he was describing what is now referred to as livedo reticularis.

In 1907, Ehrmann distinguished between the physiological livedo reticularis and a pathological form that he coined livedo racemosa.[21] The term reticularis is derived from the Latin word reticulum meaning net. The term racemosa is derived from the Latin word racemus, which means branches
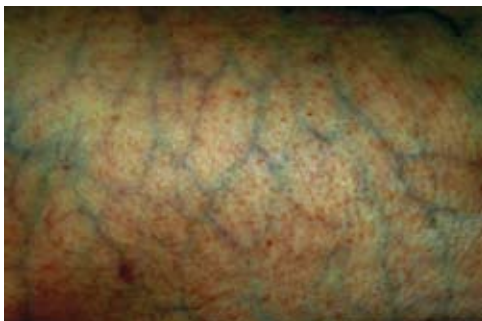
Figure 10: *Subcutaneous superficial venous plexus. Note the reticulate appearance generated by the reticular veins.*
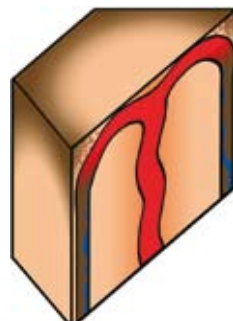
Figure 11: *Venous occlusion with minor inflammation generating purpura along the periphery of the arterial hexagon.*
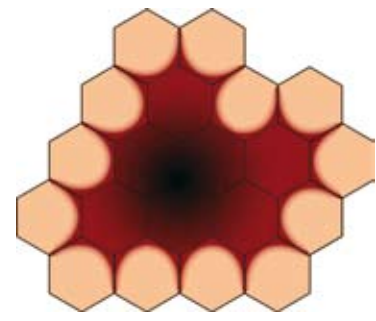
Figure 12: *Stellate pattern generated by the confluence of a number of involved hexagons.*

Figure 13: Livedo Racemosa. Note the blanched appearance at the centre of each incomplete ring & venous congestion along the rims. The branched appearance of livedo racemosa should be compared with full rings of livedo reticularis (Figure 14).

Figure 14: Livedo Reticularis secondary to venous congestion.


Figure 15: Bier's spots

of a grape. Ehrmann emphasised that livedo racemosa did not respond to warming of the skin and based on his definition, livedo racemosa implied a fixed pathological eruption that assumed a ramified shape resembling the branches of grape.

In 1936, Darier referred to livedo reticularis as livedo annularis a frigore or asphyxia reticularis.[22] In 1955, Feldaker described livedo reticularis with summer ulceration for a condition that French or German authors would have described as livedo racemosa. One year later, Feldaker and colleagues published an article titled Livedo Reticularis with Ulcerations.[23] He reported patients who had mainly developed ulcers in wintertime and termed that livedo reticularis with winter ulceration. He stated that the clinical and histopathologic findings in both summer and winter variations are very similar and pointed out that some of his patients developed ulcers both in summer and winter, but stopped at declaring both conditions as essentially the same.

In English literature, especially subsequent to a review article published in the British Journal of Dermatology by R. H. Champion in 1965,[24] livedo reticularis has come to be synonymous with the term livedo racemosa. In contrast, the German and French authors maintained the distinction between the two entities. Some European authors have even expanded the use of livedo racemosa to include all pathological conditions presenting with a reticulate pattern in contradistinction with livedo reticularis which was maintained to imply the physiological version due to cold stress. In this setting, livedo racemosa is being used to imply a secondary non-physiological livedo reticularis.

This evolution did not happen in English literature and further confusion has developed since then, with multiple terms in concurrent use. For instance, some authors use livedo reticularis to refer to both the physiological and the pathological conditions while others have used livedo reticularis symptomatica to refer to the pathological form.[25]

The physiological entity is also referred to as cutis marmorata by some authors. Our research was not successful in revealing the origin of the term cutis marmorata but the term was already in common use as far back as 1905 by dermatologists such as Ehrmann (1905 & 1907), and Lehner and Kennedy (1922).[21, 26, 27] Some authors have used cutis marmorata to imply a physiological entity and livedo reticularis to imply a pathological one.[28] Cutis marmorata is popular in paediatric literature and is consistently used to describe the physiological livedo reticularis seen in neonates as opposed to Cutis Marmorata Congenita Telangiectasia, a multi-system pathological syndrome.[29] Cutis marmorata is also frequently used in diving and aviation medicine to refer to the reversible livedo reticularis seen in type I decompression sickness.[30]
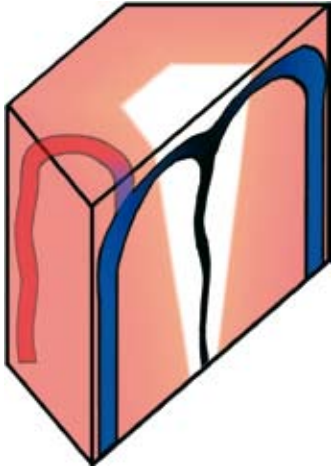
Figure 16: Atrophy of the central arterial vessel leading to hexagonal scarring typical of atrophie blanche.

Figure 18: Vasospastic Livedo Reticularis

Figure 17: Atrophie Blanche. Note the stellate pattern of scarring most likely due to infarction of small arterioles.

Figure 19: Reticulate pigmentation of livedo vasculopathy

To complicate matters further, some recent publications have advocated the use of livedo racemosa to imply a broken pattern of livedo reticularis but defining both livedo reticularis and livedo racemosa as fixed pathological entities that do not disappear on warming of the skin. For instance, in the recent update of classification criteria for Antiphospholipid Syndrome, livedo reticularis was defined as "the persistent, not reversible with rewarming, violaceous, red or blue, reticular or mottled pattern of the skin of trunk, arms or legs, consisting of regular unbroken circles (regular livedo reticularis) or irregular-broken circles (livedo racemosa)".[31] These irregular broken circles have also been termed broken pattern livedo by others.

More recently, a new approach based on the pathophysiology has appeared in dermatology textbooks. Livedo reticularis is used to imply the blanchable physiological entity and retiform or reticulate purpura as the non-blanchable fixed purpura.[32]

Terminology of Reticulate Eruptions

Medical terminology should ideally be understandable to readers of all cultural and linguistic backgrounds. This is partly why the CEAP classification of venous disease was

developed and new venous anatomical nomenclature was introduced and adopted by the society members of the Union Internationale Phlebologie (UIP).[33, 34]

Historical, geographical, and linguistic differences have generated a considerable degree of confusion in terminology used to describe eruptions with a reticulate pattern. Simplification and clarification of terminology is the task of a consensus group of experts in the field, however for the purpose of this article a simple classification system based on pathophysiology was developed.

While devising this classification, two important factors were considered. Firstly, the pattern was differentiated from the colour. What all these conditions have in common is a reticulate pattern in its complete or partial forms. This paper has retained the terms reticulate and reticularis to refer to the netlike pattern, adopted the term racemosa to refer to the branched pattern and the term localised to refer to a non-generalised pattern.

Secondly, the blanchable properties were considered. Livedo reticularis implies blanchable rings, livedo racemosa is only partly blanchable and purpura is non-blanchable.

Livedo Reticularis
[Latin: livedo (pale blue) + reticularis (netlike)]

In this paper, this term is used in its strict sense (Syn. cutis marmorata) referring to the netlike blanchable transient violet mottling of skin, usually a physiological response to cold (Figure 18) but can also be secondary to underlying conditions such as connective tissue disorders, drugs and infections (Figure 14). Livedo reticularis disappears with warming whereas with livedo racemosa may become less prominent with warming, but still persists.[35] Livedo reticularis can be classified into vasospastic (Figure 18) or venocongestive (Figure 14).

Livedo Racemosa
[Latin: livedo (pale blue) + racemosa (branched)]

This is an irregular, branched, violet discolouration of skin (Figure 22). The eruption is branched as against the netlike eruption of livedo reticularis. In contradistinction with livedo reticularis which is blanchable, livedo racemosa is partially blanchable due to its underlying inflammatory or occlusive pathology. Also, livedo racemosa is always a sign of a pathologic process, whereas livedo reticularis can be physiological. Finally, livedo racemosa differs from livedo reticularis by its histological features, and its distribution which may be segmental (as in cutis marmorata congenita telangiectasia) or localised (as in cholesterol embolisation syndrome) (Table 2) (Figure 23).[36] Widespread and generalised livedo racemosa may be confused with livedo reticularis. Livedo racemosa can progress into reticulate purpura. Localised livedo racemosa and localised reticulate purpura have both been referred to as broken pattern livedo.

Livedo racemosa results from irregular, focal and persistent impairment of blood flow due to vaso-inflammatory and/or vaso-occlusive causes. It is strongly associated with the arterial subset of Antiphospholipid syndrome (APS).[37] Livedo racemosa also occurs in disorders such as polyarteritis nodosa, systemic lupus erythematosus (SLE) with or without APS, polycythaemia rubra vera, essential thrombocythaemia, thromboangiitis obliterans, Sneddon's syndrome, cryoglobulinaemia, cold agglutinins, syphilis, tuberculosis, and cholesterol embolisation syndrome. [38] [39] [40]

Purpura

Purpura refers to haemorrhage in skin or mucousmembranes. It is by definition non-blanchable as compression will not move away the extravasated red cells, or red cells trapped in occluded vessels. By contrast, livedo reticularis is blanchable and livedo racemosa is partially blanchable.

Morphologically, it is also important to differentiate between erythema and purpura. Vasodilatation or venocongestion presenting with erythema will blanch completely. A lesion consisting of some inflammation and some haemorrhage, such as vasculitis, will blanch partially due to patency of some vessels. A lesion caused by vessel occlusion or simple haemorrhage in skin will not blanch at all.

Purpura is classified into palpable and non-palpable purpura. Non-palpable purpura is further classified into petechial (platelet based) and ecchymotic (clotting factor or vessel wall aetiology). Non-palpable purpura usually has a non-inflammatory aetiology.

Palpable purpura usually has an inflammatory aetiology. It is classified into round and reticulate (or retiform). Round lesions are usually caused by small vessel disease such as leukocytoclastic vasculitis.

Figure 20: *Reticulate pigmentation secondary to livedo vasculopathy. This patient had Protein S deficiency.*

Figure 21: *Reticulate purpura and ulceration secondary to livedo vasculopathy*

Table 2: *Reticulate Eruptions*

	Livedo Reticularis	Livedo Racemosa	Reticulate Purpura
Pathology	Can be physiological	Always pathological	Always pathological
Examples of underlying conditions	Primary: Physiologic Secondary: Connective tissue disorders	Sneddon's syndrome Embolisation syndromes	Livedo vasculopathy Antiphospholipid syndrome
Blanchablility	Blanchable	Partially blanchable	Non-blanchable
Morphology	Reticulate	Branched	Reticulate
Colour	Livid	Livid	Purpuric
Distribution	Diffuse, symmetrical	Localised or generalised	Localised or generalised
Synonyms	Cutis marmorata	Broken pattern livedo	Retiform purpura
Sub-types	Vasospastic Venocongestive	Localised Generalised	Localised Generalised

Reticulate purpura is caused by conditions affecting the medium sized vessels such as PAN and livedo vasculopathy. Both inflammatory and occlusive conditions can present with reticulate purpura. Reticulate purpura without inflammation suggests microvascular occlusion, whereas prominent erythema in early reticulate lesions suggests vasculitis.

Classification of Reticulate Eruptions

Conditions presenting with a reticulate pattern can be divided into vascular and non-vascular entities. Vascular entities presenting with a reticulate pattern can be divided into vasospastic or venocongestive, vasoinflammatory, and vaso-occlusive.

The non-vascular entities can be divided into congenital and acquired. The non-vascular entities do not necessarily have a concurrent involvement of the underlying vascular network.

Vasospastic or Venocongestive Conditions

The reticulate pattern observed in these conditions can be transitory and may disappear on re-warming. In most cases it is due to vasospasm of cutaneous ascending arterioles or congestion of the draining veins.

Livedo Reticularis (LR)

LR is characterised by a netlike formation of completely blanchable rings that may exhibit central pallor (Figure 18) and/or cyanotic rings (Figure 14). LR usually involves the extremities but may also appear on the trunk. LR becomes more intense on exposure to cold and may disappear completely on warming. It may be associated with tingling and numbness at colder temperatures. LR can be classified into vasospastic or venocongestive based on the primary underlying pathology.

Vasospastic LR

Vasospastic LR is due to decreased arteriolar inflow and presents with central pallor of individual hexagons (Figures 9 and 18). The decreased arterial inflow can lead to a decreased flow in the collecting veins that presents with cyanosis and congestion of deoxygenated venous blood along the rims of the affected hexagonal rings (Figure 9).

This condition may be associated with an underlying cutaneous or even generalised vasomotor instability and patients may present with concurrent Raynaud's disease, acrocyanosis, rosacea and flushing or even hyperhidrosis. Vasospastic LR is usually more common in females. There is usually a long history of its presence and some patients may not even be aware of its presence. Other unusual but possible causes of decreased arteriolar inflow would include increased blood viscosity and decompression sickness syndrome (DCS).[35] Vasoconstriction induced by ß-blockers can make vasospastic LR more prominent.

Vasospastic LR is one of the most important signs of DCS.[41] In this setting (Aviation and Diving Medicine), LR is usually referred to as Cutis Marmorata to emphasize its transient physiological nature. It presents with skin mottling, often on the pectoral region, shoulders, chest, or upper abdomen. Individual rings demonstrate central pallor and peripheral cyanosis. Pale areas later change to an erythematous mottling, which become 1°C to 2°C warmer. [42] The underlying cause is gas embolisation to the cutaneous

Figure 22: *Livedo racemosa in a child with Cutis Marmorata Telangiectasia Congenita (Courtesy of Dr Orli Wargon)*

Figure 23: *Livedo racemosa localised to ankles and feet*

arterial vasculature.[30] This condition is also seen with the use of both hyperbaric,[43] and hypobaric chambers.[44, 45] It usually responds well to re-pressurisation to site pressure and to hyperbaric treatment if caught early. [42]

Venocongestive LR

Venocongestive LR is due to obstructed or sluggish venous outflow. Here the rings exhibit cyanotic rims. Venocongestion can be secondary to decreased arterial inflow or due to decreased venous outflow. When secondary to decreased arterial inflow, the rings are hexagonal demonstrating central pallor. The cyanotic discolouration occurs at the anastomoses between arteriolar cones where deoxygenated blood stagnates (Figure 9).

When the pathology involves the larger reticular veins, the venous rings follow the course of the reticular veins and do not demonstrate a hexagonal arterial based formation (Figures 10 and 14).

Venocongestive LR can be caused by increased blood viscosity, drugs such as amantadine, infections such as parvovirus B19, mycoplasma and hepatitis C.

LR is an important cutaneous manifestation of parvovirus B19 infection, which can present with generalised LR and myasthenia like symptoms.[46] Mycoplasma pneumonia and hepatitis C are known to cause hyperviscosity states that can manifest as LR Brucella infection and Q fever have also been reported in association with LR.[47-49]

The synthetic antiviral agent amantadine, first introduced to prevent influenza infection, is also associated with LR.[50-53] Amantadine-induced LR is more frequent in women.[36, 52, 54] The diffuse pattern of amantadine-induced LR suggests a generalised congestion of deoxygenated blood in the superficial reticulate venous network. Amantadine is now used to treat Parkinson's disease and fatigue associated with multiple sclerosis. It causes depletion of dopamine, adrenalin and noradrenalin at the peripheral nerve terminals. For many years, this depletion of catecholamines from adrenergic nerves was thought to be the cause of amantadine induced livedo reticularis. It is now proposed that amantadine inhibits N-methyl-D-aspartic acid (NMDA) evoked release of acetylcholine in a non-competitive way and the pathogenesis of LR involves the cutaneous NDMA receptors.[55]

Many other drugs have been associated with livedo reticularis.[35] Some examples include heparin, catecholamines, quinidine, and bismuth. However, given the confusion in terminology one must be cautious in interpreting this information. Many of the reports of the so-called 'livedo reticularis' may indeed be referring to livedo racemosa or even reticulate purpura.

Cutis Marmorata (CM)

CM is synonymous with livedo reticularis. This term is used in the paediatric literature to refer to the physiologic mottled appearance observed in neonates. It should be differentiated from cutis marmorata telangiectatica congenita (CMTC) which is a pathological syndrome with multiple serious associations.

CM is the most common form of reticulate eruption seen in infants and children.[35] It is seen more commonly in pre-term infants, affecting around 50% of children.[56] CM is usually confined to the lower extremities but can be generalised.[57] If the reticulate pattern persists beyond 6 months, or does not resolve with rewarming then neonatal lupus, hypothyroidism, or CMTC should be excluded.

Cutaneous vasomotor instability is fairly common in newborns and CM is its most common manifestation. Acrocyanosis and harlequin colour change are other manifestations of vasomotor instability in neonates.

Persistent CM can be seen in Trisomy 21, Cornelia de Lange syndrome and homocysteinuria. This needs to be differentiated from CMTC.

LR associated with decompression sickness has also been termed CM to emphasize its transient physiological nature.[41]

Dirvy van Bogaert Syndrome

This condition was described in 1946 by Dirvy and van Bogaert.[58] This syndrome includes CM in association with non-calcified cerebral vascular malformations, mental retardation and spasticity. The patient may present with generalised livedo reticularis, dementia, epilepsy, and pyramidal and extrapyramidal signs. Multiple focal infarcts may be seen on MRI. Angiography demonstrates widespread cerebromeningeal angiomatosis with multiple small and medium size arterial occlusions. A lifelong personal and family history of mental handicap in the absence of anticardiolipin antibodies suggests Dirvy van Bogaert syndrome. It should be differentiated from Sneddon's syndrome.

Bier's Spots

This condition was first described by German surgeon August Karl Gustav Bier in 1898 as blanched macules that appear on the forearm and hand after the application of a tight sphygmomanometer cuff. In 1908, Bier also described intravenous regional anaesthesia, the so-called Bier block.

Bier's spots are small, irregular blanched macules, which may result in a distinct reticulate pattern most commonly observed on the limbs (Figure 15).[59] The lesions disappear with elevation of the limb.[60] If the venous stasis is reduced by raising the limb or taking off the tourniquet, the spots disappear but recur in the same areas when induced again.[60]

This phenomenon is considered to be an exaggerated physiological response to venous hypertension.[60] It has been proposed that the underlying mechanism may involve VAR vasospasm of ascending arterioles as a response to venous filling.[59] Bier's spots have been associated with other conditions such as systemic scleroderma with renal crisis,[61] and over the cyanotic abdomen of a pregnant lady, disappearing after delivery.[62] Bier's spot should be differentiated from multiple lesions of naevus anaemicus.

Marshall-White Syndrome

This syndrome is a combination of Bier's spots, insomnia and tachycardia. This syndrome has been reported more commonly in white middle-aged men with a psychiatric history.[63]

Naevus Anaemicus

Naevus anaemicus is a congenital localised vascular anomaly that presents clinically as a blanched macule or patch, first described by Vorner in 1906.[64] A mosaic formation of multiple anaemic naevi can appear reticulate (Figure 24).

Naevus anaemicus has been termed a pharmacologic naevus resulting from increased vascular sensitivity to catecholamines. This disorder has been thought to be due to a localised hypersensitivity to catecholamines. Deficient function of α-adrenergic receptors of the cutaneous blood vessels and an increased reactivity of α-adrenergic receptors leading to permanent vasoconstriction has also been proposed as the aetiology.[65, 66]

Normal colour and erythema can be induced in these lesions with an axillary sympathetic block or with intradermal injection of the α-adrenergic blocking agent, pilocarpine. Autograft exchange transplantation studies have shown donor site dominance further confirming the localisation of the pathology to the specific areas of skin.

Multiple anaemic macules of naevus anaemicus should be differentiated from localised livedo racemosa or Bier's spots. Bier's spots are transient anaemic macules whereas naevus anaemicus is a permanent anaemic lesion only reversible by pharmacological intervention.

Reticular Telangiectatic Erythema (RTE)

RTE is a skin reaction associated with implantable cardiac devices such as pacemakers and cardioverter defibrillators,[67] and intra-thecal drug delivery systems.[68] It presents with a reticulate macular erythema with poorly defined margins and telangiectasias overlying the implanted device. It can eventually lead to erosion of the skin overlying the device.[68]

Figure 24: *Segmental unilateral naevus anaemicus presenting as a reticulate eruption*

Although initially thought to be caused by heat and electric or magnetic fields generated by cardiac devices, the observation of the same condition associated with an infusion pump has effectively disproved these hypotheses and the cause is currently unknown.

Reticulate Lymphoedema

In 1996, Cox et al[69] reported 8 patients presenting with lymphoedema with prominent compressible ridges of tissue in a reticulate pattern. They called this condition 'lymphedema ab igne' as it mimicked erythema ab igne.

Vasoinflammatory Conditions

Vasculitis is an inflammatory disorder of blood vessels that can affect vessels of any size or type in any organ.

The most widely used classification of vasculitis is based on the vessel size (small, medium and large) (Table 1).[1] There is considerable overlap between the three groups. Small vessel vasculitis usually presents with round lesions of palpable purpura. Examples include leukocytoclastic vasculitis (Figure 25) and Henoch-Schönlein purpura.

Large vessel vasculitis can present with dissection or aneurysm of the vessels involved. Skin and visceral involvement is less common in large vessel vasculitis. Examples include Temporal (giant cell) arteritis and Takayasu's arteritis.

Involvement of the medium sized vessels may induce a reticulate pattern (Figure 26). The eruption can first present with the partly blanchable livedo racemosa but may progress onto the non-blanchable reticulate purpura. Deposition of immunoglobulins in the vessel walls and intraluminal deposition of fibrinogen and complements impedes the flow and presents with the partly blanchable livedo racemosa. The subsequent fibrin deposition, thrombotic occlusion and red cell extravasation presents as the non-blanchable reticulate purpura. These two processes are not mutually exclusive and the same patient may have concurrent evidence of both. Furthermore, concurrent involvement of small vessels will further complicate the clinical picture by the presence of palpable purpuric lesions of small vessel vasculitis.

Polyarteritis Nodosa (PAN)

PAN was first described in 1866 by Kussmaul and Meier who reported palpable nodules along the course of the affected arteries. PAN is a vasculitis of medium-sized

Figure 25: *Lesions of palpable purpura of leukocytoclastic vasculitis. Note that these lesions do not blanch.*

Figure 26: *Medium and small sized vessel vasculitis presenting with a reticulate eruption*

arteries and can be classified into the classic systemic PAN, microscopic polyangiitis (MPA) and cutaneous PAN.

Classic PAN is a systemic vasculitis characterised by necrotizing inflammatory lesions affecting predominately medium and small muscular arteries. It can involve the heart, liver, kidneys, gastrointestinal tract (GIT) and the nervous system. The vasculitis preferentially affects the vessel bifurcations, resulting in microaneurysm formation, thrombosis and organ infarction. The damaged vessels are

very prone to aneurysmal rupture with haemorrhage. The 5 year survival rate is 50% and death occurs due to involvement of kidneys or GIT.[70] The skin is involved in 10-15% of cases of systemic PAN resulting in palpable purpura, nodules, and ulcerations. Other symptoms such as fever, weight loss, fatigue, arthralgia, myalgia, and intestinal angina may be present.[71]

Classic PAN

Classic PAN should be differentiated from MPA. By definition, classic PAN does not affect arterioles, venules, or capillaries (hence no glomerulonephritis) whereas involvement of microscopic vessels must be present in microscopic polyangiitis, although medium sized or small arteries can also be involved.[1] Involvement of medium-sized arteries is always present in PAN but may also occur in MPA. Necrotizing glomerulonephritis and pulmonary capillaritis often occur in MPA. The term microscopic polyangiitis was preferred over microscopic polyarteritis due to involvement of venules and capillaries.

Cutaneous PAN

Cutaneous PAN is a vasculitis of the small- and medium-sized arteries in the reticular dermis and subcutaneous tissue.[72] Cutaneous changes are most common in the legs and can be extremely painful. It can present with LR or livedo racemosa (Figure 27) and sometimes reticulate purpura and can even progress into ulceration. Palpable purpura develops in a small group of patients due to involvement of smaller vessels. Livedo racemosa can have a diffuse distribution over arms, legs and buttocks, and does not completely blanch when pressure is applied to the skin.[71] Livedo racemosa, nodules and ulceration can localise to the medial ankle area. The ulceration can lead to typical lesions of atrophie blanche.[73] PAN should be excluded in patients presenting with atrophie blanche without evidence of chronic venous insufficiency (CVI) or LV, particularly in the presence of mononeuritis multiplex.[73]

Detection of anti-neutrophil cytoplasmic antibodies (ANCA), a class of antibodies identified by immunofluorescence, may be a useful investigation in patients with vasculitis. Only 10-20% of patients with PAN have positive ANCA findings, the peripheral pattern (p-ANCA) more so than the diffuse cytoplasmic pattern (c-ANCA).[74] ANCA is reported to be a sensitive marker for Wegener's granulomatosis (c-ANCA), MPA (p-ANCA) and some cases of classic PAN.[72, 75]

Figure 27: *Livedo racemosa in a child with polyarteritis nodosa (PAN) (Courtesy of Dr Orli Wargon)*

Antiphospholipid Syndrome (APS)

This condition has been previously reviewed in this journal.[76] It is characterised by hypercoagulability with recurrent thromboses in veno-arterial circulation and commonly thrombocytopenia. Deep vein thrombosis (DVT), pulmonary embolism (PE), recurrent miscarriages and cerebrovascular accidents are all manifestations of APS. The revised criteria for its diagnosis were published in 2006.[31]

Reticulate eruptions in patients with APS are associated with development of arterial ischaemic events.[77-79] Livedo racemosa is one of the presenting sign of APS in up to 40% of patients (Figure 28).[80, 12] Reticulate keloidal purpura associated with transient antiphospholipid antibodies and hyper-homocysteinaemia was reported by the author (Figure 29).[81] Reticulate and stellate acral pigmentation has been described in a patient with SLE and a high titre of anticardiolipin IgG antibodies.[82]

Sneddon's Syndrome

In 1965, Ian Bruce Sneddon described 6 patients with "cerebro-vascular lesions and livedo reticularis".[38] His patients had neurologic signs and symptoms such as weakness, hemiplegia, hemianopia and aphasia. None of the patients had features of PAN or LV. The accompanying photographs published in Sneddon's article show the branched pattern of livedo racemosa.

Sneddon and others suggested that this condition may be the result of an arteriolitis, even though they noted similarities

Figure 28: *Livedo racemosa in a patient with antiphospholipid syndrome*

Figure 29: *Keloidal reticulate purpura in a patient with antiphospholipid syndrome and hyper-homocysteinemia*

with PAN. In 1992, Zelger and colleagues demonstrated that small to medium-sized sub-dermal arteries are involved in Sneddon's syndrome, but not the arterioles or venules.[83] The same authors later on acknowledged that Sneddon's syndrome and LV may appear together.[84] Both Sneddon's syndrome and LV may be accompanied by livedo racemosa, and both conditions have been encountered in patients with SLE.

Sneddon's syndrome is associated with ischemic cerebrovascular lesions and extracerebral arterial and venous thromboses. It is a rare progressive disorder with incidence of 4 cases in every million per year affecting mostly females.[85] Antiphospholipid antibodies, anti β_2

glycoprotein antibodies, and anti-prothrombin antibodies have been detected in some patients.[10] This syndrome starts as an inflammatory and possibly immunologically mediated disorder and leads to migration and proliferation of smooth cells of small arteries, resulting in partial or complete narrowing of the vessel lumen.[85] Thickening of vessel walls and vascular occlusion have been reported from biopsies obtained from the centre of the hexagons forming the reticulate pattern.[86]

Herman's Syndrome

Herman's syndrome is reported to be a post-traumatic vasomotor syndrome after brain-injuries. It presents with livedo racemosa, pyramidal and extrapyramidal symptoms, speech disorders, epileptic seizures and progressive dementia. It is mostly reported in the Polish neurological literature.[87,88] Herman's syndrome may be a variation of Sneddon's Syndrome.[89]

Vaso-occlusive Conditions

Occlusion of cutaneous blood vessels is uncommon and can present with a range of clinical pictures. The occlusion can be a primary event or secondary to inflammation (vasculitis). Vaso-occlusive conditions may initially present with livedo racemosa, which may progress into purpura, necrosis and ulceration. Patients with secondary vascular occlusion may present with signs of the underlying inflammatory process which will produce a mixed clinical picture to include a combination of livedo racemosa, lesions of palpable purpura, reticulate purpura, reticulate pigmentation, infarction, ulceration and atrophie blanche.

Vascular occlusion can be caused by cells, blood components, foreign organisms, drugs, crystals and sludge. Some important examples include platelet rich thrombi as in thrombocythaemia, fibrin thrombi seen in warfarin necrosis, emboli as in cholesterol emboli, immunoglobulins seen in cryoglobulins, swollen endothelial cells containing numerous acid fast bacilli as in Lucio's phenomenon of leprosy, fungi seen in mucormycosis and sludge induced by drugs such as sclerosants. Vascular intimal hyperplasia can cause partial obstruction presenting with Livedo Racemosa.

A) Red Blood Cells

Polycythaemia rubra vera has been associated with livedo reticularis.[90]

B) Platelets

Occlusive conditions affecting platelets include thrombocythaemia, Heparin Induced Thrombocytopaenia Syndrome (HITS), and myeloproliferative disorders.

Thrombocythaemia can lead to disturbances in microvascular circulation caused by spontaneous activation and aggregation of hypersensitive platelets at conditions of high shear stress.[91] Related cutaneous manifestations have been reported to include livedo racemosa and haemorrhagic manifestations such as petechiae, ecchymoses and haematomas. Other manifestations include erythromelalgia, acrocyanosis, recurrent superficial thrombophlebitis, and ischemic complications with gangrene, leg ulcers, or ulcers on the toes.[92]

C) Thrombus

Thrombus in the superficial vascular plexus can cause occlusion of the involved vessels presenting with reticulate purpura or necrosis. Predisposing conditions include hypercoagulable states such as inherited and acquired thrombophilias, sepsis and malignancy. Conditions presenting with primary microvascular thrombotic occlusion include LV, warfarin induced skin necrosis, calciphylaxis, disseminated intravascular coagulopathy (DIC), and paroxysmal nocturnal haemoglobulinuria. Thrombophilia itself can present with microvascular thrombosis and reticulate purpura (Figure 20).

Livedo Vasculopathy (LV)

In 1966, Gray and colleagues introduced periodic painful ulcers of lower extremities as a synonym for atrophie blanche.[93] Their published images show thrombi in the lumina of dermal vessels, a finding typical of what is now known as LV.

One year later, Bard and Winkelmann coined the term livedo vasculitis but synonymously used segmental hyalinizing vasculitis to refer to the same condition.[94] They used the latter having noticed hyalin material in the biopsy specimens although what they pictured appears to be fibrin in the vessel walls.

In 1974, Winkelmann and colleagues referred to the same condition with three different names: segmental hyalinizing vasculitis, livedo vasculitis, and livedoid vasculitis.[95] They noted that some of the patients diagnosed previously as livedo reticularis with summer or winter ulcerations or as atrophie blanche probably had the same condition.

In 1992, McCalmont and colleagues used the term livedo vasculopathy instead of vasculitis noting the absence of true vasculitis and the thrombogenic nature of the condition.[96] The same condition was referred to as livedoid vasculopathy by Jorizzo in 1998.[97]

LV is characterised by ulceration associated with livedo racemosa and atrophie blanche. It occurs principally on the lower legs and ankles of young to middle aged women but can commence in childhood. Dermatological manifestations include reticulate purpura, pigmentation and ulceration (Figure 21).

The eruption can start with small purpuric macules or even haemorrhagic bullae. Some lesions heal without further progression but others become necrotic and coalesce to form reticulate ulcers. The lesions can be quite painful and the clinical features can closely resemble pyoderma gangrenosum. Healing takes place over several weeks or months and may leave atrophie blanche type scarring with surrounding erythema and hyperpigmentation (Figure 30). LV is not associated with CVI but lipodermatosclerosis can occur concurrently.

LV is a thrombo-occlusive disease. Histologically, it shows fibrin thrombi within the wall and the lumen of the affected vessels, but there is no true vasculitis. There is strong evidence for a procoagulant pathogenesis.[98] Factor V Leiden mutation, prothrombin gene mutation, protein C deficiency, hyper-homocysteinaemia, other inherited thrombophilias, abnormalities in fibrinolysis, and increased platelet activation have all been associated with LV.[99] Tissue plasminogen activator (tPA) levels appear to be lower possibly due to defective release and plasminogen activator inhibitor-1 (PAI-1) levels appear increased.[100, 101] A high incidence of antiphospholipid antibodies has been reported in patients with LV.[101] Case reports of successful treatment with anticoagulant, anti-platelet and fibrinolytic therapy utilising low molecular weight heparin (LMWH), warfarin, aspirin, and tPA have appeared in the literature.[102]

Atrophie Blanche

In 1929, the French dermatologist Milian used the term atrophie blanche [French: atrophie (atrophy) + blanche (white)] to refer to small white atrophic scars of the lower legs. He classified this condition amongst what he termed les capillarites, a term he defined as "inflammation of lymphatics, arterioles, or venules".[103] Milian divided atrophie blanche into two types, a localised variant that he termed atrophie blanche en plaque, and a more extensive form that he called atrophie blanche segmentaire. The segmental

variant would imply the involvement of an entire foot or even a large segment of the leg.

The designation atrophia alba was used by Schuppener, in 1957, as a synonym for atrophie blanche in an article published in German.[104] The description of Schuppener is very similar to what is known today as livedo vasculopathy. Some physicians still use atrophie blanche synonymously with livedo vasculopathy.
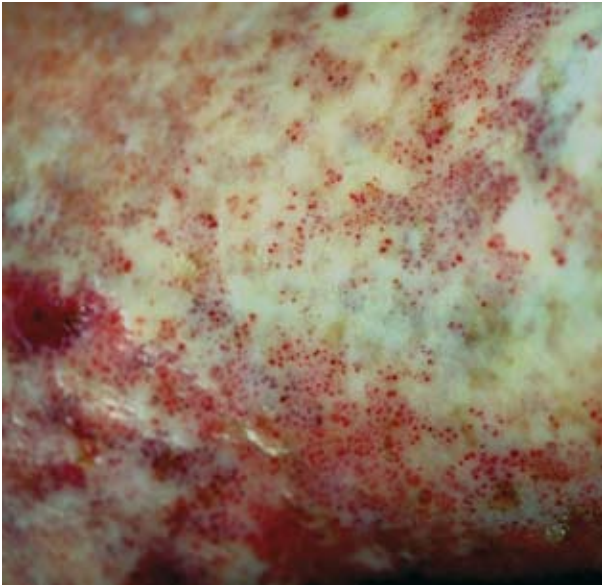
Figure 30: *Close up view of atrophie blanche and re-vascularisation of the scarred tissue.*

Atrophie blanche is characterised by porcelain white, smooth, atrophic scars interspersed by punctate telangiectasias (Figures 17 and 30). The white cast of the lesions is caused by sclerosis of the upper dermis. Lesions are similar to those found in Degos disease, which develop consequent to occlusion of an arteriole in the dermis (Figures 16 and 17). The individual lesions can be hexagonal but when confluent, large areas demonstrate the porcelain white scarring. A reticulate pattern of scarring is caused by the presence of multiple lesions (Figure 30).

Atrophie blanche is the end stage of LV, CVI and vasculitic conditions such as leukocytoclastic vasculitis and PAN. In patients presenting with atrophie blanche without evidence of CVI or LV, underlying vasculitis such as PAN should be excluded. PAN should be particularly suspected if mononeuritis multiplex is present. Repeated and deep biopsies may be required to reveal the diagnosis.[73]

Other systemic diseases such as SLE, rheumatoid arthritis, and Klinefelter syndrome can result in skin ulcerations that heal with atrophie blanche-like lesions. Atrophie blanche type scars have also been reported consequent to the use of Interferon α therapy for melanoma.[105]

Warfarin Necrosis

Warfarin induced skin necrosis is a thrombohaemorrhagic event which develops within 1-10 days of the commencement of warfarin therapy. It is more common in middle-aged, peri-menopausal, obese women and affects the fatty areas of thighs, buttocks, and breasts (Figure 31). The initial skin manifestation is livedo racemosa, which can rapidly progress into a segmental pattern of reticulate purpura (Figure 32) and then a catastrophic tissue necrosis (Figure 33).

Warfarin necrosis occurs in patients with thrombophilic abnormalities and in particular patients who are protein C or S deficient.[106] It is a caused by a transient imbalance between procoagulant and anticoagulant serum factors. Procoagulant factors II (prothrombin), VII, IX and X and the anticoagulant proteins C and S are all synthesised in the liver requiring the reduced form of vitamin K. Protein C circulates as an inactive zymogen in blood and requires thrombin and thrombomodulin for activation. The activation of the anticoagulant protein C by the procoagulant thrombin is known to regulate the process of coagulation. Activated protein C (APC) inhibits coagulation factors Va and VIIIa. Protein S is a non-enzymatic cofactor of APC. Warfarin inhibits vitamin K epoxide reductase, hence preventing the re-synthesis of the reduced vitamin K. This decreases the levels of vitamin K-dependant procoagulant factors (hence the anticoagulant effect of warfarin) as well as a moderate decrease in protein C and S

Figure 31: *Warfarin necrosis*

Figure 32: *Livedo racemosa and purpura in a patient with Warfarin necrosis secondary to acquired protein C deficiency at an early stage.*

Figure 33: *Same patient as Figure 32 demonstrating massive tissue necrosis 2 days later.*

levels. The lowering of protein C level occurs much earlier, as the half-life of protein C is much shorter compared with most of the procoagulant factors (protein C, 14 hours vs. factor IX, 24 hours; factor X, 40 hours; factor II 60 hours). In protein C-deficient individuals, the protein C baseline levels are lower, which causes a temporary exaggeration of the imbalance between procoagulant and anticoagulant factors leading to a relative hypercoagulable state. This leads to thrombotic occlusions of the microvasculature with resulting necrosis. The effect of warfarin combined with a transient deficiency of vitamin K dependant clotting factors leads to a haemorrhagic state. Therefore warfarin necrosis is a thrombohaemorrhagic event.

Most reported cases of warfarin necrosis, which number about 300, have been associated with hereditary protein C deficiency. A small number of cases have been associated with other thrombophilic abnormalities such as protein S deficiency, factor V Leiden mutation, antithrombin III deficiency and circulating antiphospholipid antibodies.[106]

Large loading doses of warfarin can significantly reduce the protein C and S levels and should be avoided. In patients with known protein C or S deficiency, warfarin dose should be increased gradually (by 1-2 mg per day) and over an extended period of time to avoid a rapid depletion of these anticoagulant factors and the subsequent tissue necrosis.[107]

Disseminated Intravascular Coagulation (DIC)

DIC is an acquired syndrome characterised by the intravascular activation of coagulation with loss of localisation of the thrombotic process resulting in the generation and deposition of fibrin thrombi in the microvasculature.[108] Widespread deposition of microvascular thrombi can cause multi-organ failure. The widespread generation of fibrin thrombi can cause consumption of platelets and clotting factors which then leads to a haemorrhagic state. Hence, DIC can be defined as a thrombohaemorrhagic disease.

DIC is not an independent disease and its presence always indicates an underlying condition. Some of the more common underlying causes include bacterial septicaemia, severe trauma, solid tumours or haematological malignancies, obstetric complications, and large vascular anomalies such as kaposiform haemangioendotheliomas (KHE) leading to Kasaback-Meritt syndrome. These underlying conditions cause a number of coagulation abnormalities that combine to induce DIC. These abnormalities include (1) generation of thrombin and tissue factor, (2) impaired coagulation inhibitor system, and (3) impaired fibrinolysis.

DIC can present with multiple cutaneous signs. Deposition of thrombi in the microvasculature can present with reticulate purpura and necrosis. Platelet consumption and the subsequent thrombocytopenia will present with petechiae on the soft palate and lower limbs. The depletion of clotting factors will present with ecchymosis at the venipuncture sites and traumatised areas. Purpura fulminans, localised infarction and gangrene may occur. Heparin-associated thrombocytopenia has been reported to cause DIC resulting in thrombotic occlusion of cutaneous blood vessels presenting with "livedo reticularis".[109]

Thrombotic Microangiopathies (TMA)

TMA include haemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). The clinical triad of renal failure, thrombocytopenia, and microangiopathic haemolytic anaemia is considered the hallmark of TMA syndromes. The pathologic hallmarks

of TMA include vessel wall thickening, endothelial cell swelling, intraluminal platelet thrombi, and microvascular obstruction. Microvascular occlusion can lead to livedo racemosa and eventually reticulate purpura. A reticulate eruption secondary to a HUS has been reported in association with the chemotherapeutic agent gemcitabine.[110]

D) Emboli

Vascular occlusion can be caused by emboli arriving from distant sites. Potential sources include thrombi, lipids and infections. For example, arterial thrombi embolising distally and lodging into the acral microvasculature will induce reticulate purpura and necrosis.

Cholesterol Embolism Syndrome (CES)

CES occurs most frequently in elderly white men with a history of advanced atherosclerotic disease undergoing an invasive vascular procedure such as cardiac catheterisation or receiving anticoagulant or thrombolytic therapy. In most cases, manipulation of the arterial vessels causes the dislodgement of cholesterol crystals or larger atherosclerotic plaques. Occasionally CES occurs spontaneously.[111]

The dislodgement of cholesterol crystals causes microvascular occlusion. Crystals break off from larger plaques showering into downstream organs and occlude small end-organ arterioles. This can induce an acute inflammatory reaction which eventually occludes the vessel lumen. The subsequent tissue ischemia can cause an irreversible organ damage. Organs more commonly involved include kidneys and the gastrointestinal system.[35]

Dislodgement of larger atherosclerotic plaques can occlude larger arteries, causing tissue infarction and acute organ failure. Causes include local trauma to the individual plaques such as that caused by angiography, aortic trauma, destabilisation of the clot overlying the plaque, anticoagulation and thrombolytic therapy.

Skin manifestations include pain and tenderness at the site of lodgement and livedo racemosa which develops into a segmental pattern of reticulate purpura and necrosis.[77, 112, 113] Cutaneously, this condition affects the thighs (and especially the knees) in 60%, the trunk in 30% and arms in only 8%.[113] Other skin signs include infarction of perineal area, ischemic patches involving lower extremities more often than upper, blue toe syndrome and splinter haemorrhages.

Biopsy of purpuric skin lesions has a high diagnostic yield of more than 90%.[113] This is important because, although CES frequently presents as a multi-systemic disease, cutaneous findings may often be the only clues to the diagnosis. All patients with the classic triad of livedo racemosa, acute renal failure, and eosinophilia should be evaluated for CES, including an eye examination.

Septic Embolism

Dislodged thrombi containing micro-organisms are called septic emboli. These usually arise from vegetations in the heart, or infected cardiac or vascular stents. Septic emboli can also be dislodged from a peripheral vein with infective thrombophlebitis. The underlying infection can be bacterial (mostly gram negative) or fungal. Lodgement of these emboli in the cutaneous microvasculature can present with livedo racemosa, reticulate purpura or necrosis. Individual stellate ulcerations can be seen.

Septic emboli arising from the left heart can lodge into the arterial microvasculature presenting with cutaneous signs, neurological complications and organ infarction.[114] These are commonly associated with mitral valve vegetations. Instrumentation can cause pseudoaneurysms seeded with bacteria presenting with ipsilateral, distal or acral livedo racemosa.[35,115] Infections of metallic endovascular stents are potentially life-threatening requiring urgent surgical intervention.[116]

Septic emboli arising from the right heart or the venous system can lodge into the lungs causing septic pulmonary embolism or through a patent foramen ovale can lodge into the cerebral circulation. This happens most commonly in the setting of tricuspid valve endocarditis or the peripheral veins, where the underlying process is a septic thrombophlebitis. Less common sources for septic emboli include septic thrombophlebitis of pelvic veins and infected arteriovenous shunts.

CT appearance of septic emboli in the lungs includes nodules and wedge-shaped sub-pleural opacities with or without cavitation and the feeding vessel sign. This sign, which may also be seen in pulmonary metastases, consists of a distinct vessel leading directly into the centre of a nodule. This sign has been considered highly suggestive of septic embolism, the prevalence varying from 67-100% in various series.[117]

E) Immunoglobulins and Other Blood Components

Cryoglobulins

Cryoglobulins are circulating immunoglobulins complexed with other immunoglobulins or proteins that undergo reversible precipitation at low temperatures.[118] Cryoglobulins can lodge into cutaneous vascular plexus and present with

localised reticulate purpura and necrosis. Cryoglobulinemia can be idiopathic (essential cryoglobulinemia) or secondary to lymphoproliferative, autoimmune, or infectious diseases. Skin manifestations include purpuric erythematous macules and papules (90-95%), livedo racemosa, reticulate purpura and necrosis, cold-induced urticaria, Raynaud's phenomenon, acrocyanosis, ulceration, and gangrene.[119] Acral locations (feet, hands, tip of the nose, pinnae of ears) are commonly affected.

Classification of Cryoglobulinaemias

Cryoglobulinemia are classified based on the cryoglobulin composition into three sub-types.

Simple cryoglobulins (Type I cryoglobulins) consist of a single monoclonal immunoglobulin. This can be IgG or IgM and is often associated with haematological malignancies, such as multiple myeloma or B-cell lymphoma. These patients may present with a non-inflammatory occlusive vasculopathy.

Mixed cryoglobulins (Type II and Type III) are immune complexes consisting of rheumatoid factor (RF), complexed with IgG. The actual RF is usually IgM and may be monoclonal (in type II cryoglobulinemia) or polyclonal (in type III cryoglobulinemia). Types II and III cryoglobulinemia represent 80% of all cryoglobulins. Patients with mixed cryoglobulinemia typically present with inflammatory vasculitis and glomerulonephritis.[118]

Cryofibrinogens

Cryofibrinogens are protein complexes that precipitate in both cooled serum and plasma. They consist of fibrin, fibrinogen or fibrin split products complexed with plasma proteins or immunoglobulins.[120] Cryofibrinogenaemia is an extremely uncommon disorder that can be idiopathic or secondary to connective tissue disease, infections, malignancies, and thromboembolic disorders. It is more frequently found in patients with cryoglobulinaemia. The pathogenesis of cryofibrinogenaemia is unknown. It maybe caused by the inhibition of fibrinolysis, leading to the accumulation of cryofibrinogen.[121]

Skin manifestations include livedo racemosa, reticulate purpura and necrosis, and gangrene. It may clinically simulate calciphylaxis, presenting in patients with end stage renal disease. Cerebrovascular accidents, myocardial infarction, thrombophlebitis, pulmonary emboli and retinal artery thrombosis have been reported and correlate directly with the level of circulating cryofibrinogenemia.[120]

Cold Agglutinins

Cold agglutinins are usually IgM antibodies (less frequently IgA or IgG) that agglutinate and destroy red blood cells (RBCs) and result in haemolytic anaemia.[35] The specific IgM antibody is directed against the I/i antigens (precursors of the ABH and Lewis blood group substances) on RBCs. Slowing of blood flow with occlusion of superficial blood vessels by agglutinated RBCs can cause acrocyanosis, livedo racemosa and Raynaud's phenomenon.[122] These immunoglobulins can be secondary to infection or a lymphoproliferative disorder.[35] A common complaint is painful fingers and toes with purplish discolouration associated with cold exposure.

F) Infections

A number of infections can present with a reticulate eruption. The eruption may be (1) the blanchable livedo reticularis as in parvovirus B19 infection, (2) the partly blanchable livedo racemosa as in hepatitis C associated APS, (3) the non-blanchable reticulate purpura of meningococcemia or the hepatitis C associated cryoglobulinemia, and (4) the pigmented reticulate eruption of secondary syphilis, the so called 'leukoderma colli syphilliticum'.

Reticulate purpura signals an underlying vaso-occlusive process induced by the infection. The vascular occlusion may result from (A) the direct invasion of vessels by the organisms as in meningococcal meningitis or (B) indirect occlusion secondary to (1) thrombus as in sepsis induced DIC, (2) septic emboli secondary to bacterial endocarditis or (3) immune complex deposition as in hepatitis C induced cryoglobulinemia.

Occlusion of superficial vascular plexus may cause a severe inflammatory reaction, as in meningococcemia, or in a minimal reaction, as in ecthyma gangrenosum. Reticulate purpura is an indication of an acute occlusive and possibly thrombotic angiopathy and in a febrile unwell patient may rapidly progress into purpura fulminans. Apart from meningococcal meningitis, other bacterial infections such as staphylococcal, pneumococcal, or other Gram-negative septicaemia can present with a purpuric reticulate rash indistinguishable from that seen in meningococcal disease. An example is *Capnocytophaga canimorsus* infection which can cause a life threatening reticulate purpura.[123]

Meningococcal Meningitis

Meningococcal meningitis caused by *Neisseria meningitidis* can present with an abrupt onset of fever, typical neurological signs and multiple purpuric skin lesions.[78,79,124]

The eruption may start as small, scattered pinpoint petechial lesions but may rapidly progress into larger hexagonal, non-blanchable purpuric lesions appearing on lower limbs and at pressure points. The overall eruption may appear reticulate with individual hexagons demonstrating central purpura. Generalised ecchymosis, purpura fulminans, skin necrosis, and limb ischemia may follow.[78,124,125] The purpuric rash commonly fades in a few days but may be succeeded about a week after the onset of the illness by a vesicular rash which often ulcerates.

Purpuric lesions of meningococcaemia are usually larger and darker than pinpoint petechiae of thrombocytopenia, petechiae induced by vomiting or coughing or the lesions of palpable purpura associated with leukocytoclastic vasculitis. The lesions can also appear on mucous membranes and sclera.

Biopsy samples from dermis demonstrate the presence of meningococci in and around the microvascular endothelial cells. These can be cultured for up to 12 hours after effective antibiotic treatment is commenced.[126]

80% of bacteriologically proven cases of meningococcal disease develop a rash at some stage but the presence of a characteristic purpuric rash is highly variable.[127] The rash may not be purpuric early on but usually becomes so later.[128,129] The early rash may be maculopapular and can even look like insect bites. A non-purpuric maculopapular rash is a typical feature of primary meningococcal arthritis which is a rare manifestation of meningococcal disease.[130] The presence of non-purpuric lesions has been associated with delays in diagnosis,[131] and may also be confused with the maculopapular exanthem associated with penicillin sensitivity.[132] The purpuric rash however, is associated with a higher mortality rate.[133]

One of the complications of meningococcal meningitis is DIC but the characteristic purpuric rash of meningococcaemia may occur without DIC. The presence of large ecchymotic lesions (diameter >10 mm) and cold cyanosed extremities may be an indication of an underlying severe DIC and cardiovascular shock.[134]

Viral infections such as enteroviral infections, bacterial infections such as brucellosis and ricketsial infections such as Q fever caused by *Coxiella burnetti* can all present with fever and a similar petechial rash.[135] However, fever and a non-blanching purpuric rash should always prompt a serious consideration of the diagnosis of meningococcal disease.[127]

G) Drugs

A number of drugs have been associated with reticulate purpura and necrosis. Propylthiouracil has been reported in association with thrombohaemorrhagic segmental purpuric vasculitis.[136] The chemotherapy agent Gemcitabine can cause intravascular fibrin deposition when used long term and results in a thrombotic microangiopathy and haemolytic uremic syndrome associated with reticulate purpura.[110] Acetazolamide drug eruption can appear reticulate (Figure 34).

Nicolau syndrome

Also called embolia cutis medicamentosa and livedo-like dermatitis, was first described by Nicolau in 1925 following the use of bismuth salts for the treatment of syphilis.[137] It is a well recognised complication of intramuscular or intra-articular injections characterised by severe pain and cyanotic reticular lesions at the injection site, which in many cases lead to necrotic ulcers and scarring. Nicolau syndrome is due to inadvertent intra-arterial or peri-arterial administration of the offending drug with subsequent arterial spasm and cutaneous necrosis.[138] There may be burning and stabbing pain while the injection is being administered. The first visible sign is pallor, followed by a cyanotic reticulate erythema.[138]

Within a few days, the area becomes haemorrhagic, forms a necrotic eschar and leads to punched out and stellate ulceration (Figure 35). Eventually the ulcer heals leaving behind atrophic scars. Some of the implicated drugs include penicillin,[139] corticosteroids,[140] diclofenac,[141] and vaccines.[142]

Figure 34: *Acetazolamide drug eruption with a reticulate pattern*

Sclerosants

Sclerosants can induce vascular obstruction if directly injected into arteries or indirectly by inducing VAR vasospasm.[14] The mechanism of the induced necrosis is probably very similar to that of Nicolau syndrome.

The early lesion may appear with a stellate pattern of purpura formed of multiple cyanotic hexagons (Figure 36). The individual hexagons will demonstrate central purpura and eventually necrosis (Figures 37 and 5). This is in contrast with vasospastic conditions in which the individual hexagons demonstrate peripheral cyanosis and central blanching (Figure 9). In most cases, ulceration is inevitable.

H) Minerals and Crystals

Various crystals can deposit in vessel walls and cause occlusion. Important examples include calciphylaxis and oxalosis.

Calciphylaxis

This is a potentially life-threatening disorder that can present with soft tissue necrosis and ulceration.

Early changes may be subtle and the only cutaneous manifestation may be livedo racemosa caused by deposition of calcium phosphate crystals in the microvasculature (Figure 38). Livedo racemosa is usually followed by the development of asymptomatic subcutaneous calcified nodules. These calcific vascular lesions are long-standing and asymptomatic but they appear to increase the risk of thrombotic occlusion. Patients with thrombophilic abnormalities and in particular those with inherited protein C or S deficiency or acquired deficiency secondary to sepsis are at increased risk of cutaneous necrosis.[143] An acute

pro-thrombotic state will induce thrombotic occlusion of already calcified vessels that can lead to tissue necrosis. The presentation may be similar to warfarin necrosis and both conditions share similar underlying thrombophilic abnormalities. The lesions occur more frequently in the lower limbs and are extremely painful.[144,145] The associated pain has a combined ischemic and neuropathic origin.

Histological features of the pre-calciphylaxis calcific angiopathy include microvascular calcification with intimal hyperplasia and narrowing of the lumens. With thrombotic occlusion, fibrin thrombi can be visualised within the vessel lumen. With the development of ischemia, necrosis of epidermis and dermis occurs. There may be associated widespread calcification of the subcutaneous septae and concurrent ossification.[145] Calcium containing deposits have been found in the medium sized vessels as well as within the lumen of subcutaneous arterioles and capillaries.[146]
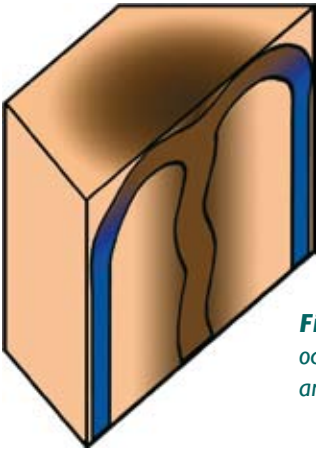
Prognosis is frequently poor once calciphylaxis is diagnosed and is worse for patients with lesions involving the trunk and proximal limbs, or for those with visceral organ involvement.[147] Gangrene with amputation and sepsis leading to death are the possible catastrophic outcomes. It is important that physicians consider Calciphylaxis in the differential diagnosis of livedo racemosa as early detection may prevent these catastrophic outcomes.

Calciphylaxis was first reported by Bryant and White in 1898 as a case of calcification of the arteries and obliterative endarteritis in association with hydronephrosis.[148] The term calciphylaxis was coined by Hans Selye in 1962 who defined calciphylaxis as a hypersensitivity reaction in which acute local calcinosis occurs followed by inflammation and sclerosis.[149] He and co-authors postulated that specific calcifying

Figure 36: *Single lesion of stellate purpura post sclerotherapy of the inter-saphenous vein complicated by veno-arteriolar reflex (VAR) vasospasm of the small saphenous artery*

Figure 35: *Nicolau syndrome (Courtesy of Dr Glenda Wood and Dr Linda Martin)*

Figure 37: *Arterial occlusion at the centre of the arterial hexagon.*

Figure 38: *Livedo racemosa secondary to vessel ossification and calcification*

factors such as vitamin D may induce sensitisation. We now know that this condition is not due to a hypersensitivity reaction and therefore the term calciphylaxis is a misnomer. The proposed alternative names have included Calcific Uremic Arteriopathy, Calcifying Panniculitis, Metastatic Calcinosis Cutis, Necrotising Panniculitis and Vascular Calcification–Cutaneous Necrosis Syndrome.[150,151,152] None of these designations are accurate or comprehensive. For example, Calcific Uremic Arteriopathy is not correct as the calcification process is not limited to arteries or arterioles and has also been reported in venous vessels.[146] Furthermore, there are case reports of patients with Calfic Angiopathy (CA) with no renal disease.[147] Calcifying Panniculitis is not accurate as panniculitis is not the primary process and may be absent. Metastatic Calcinosis Cutis is not accurate as calcified vessels may be limited to subcutis with no dermal involvement, and the calcinosis itself may

be dystrophic and not metastatic. Necrotising panniculitis is a general description of many panniculitic conditions that can present with necrosis and not specific to calciphylaxis. Vascular Calcification–Cutaneous Necrosis Syndrome is a reasonable designation but may imply the involvement of larger arteries and for the same reason Calcific Vasculopathy is inappropriate. In this article, we used Calcific Angiopathy to refer to the pre-necrotic stage of calciphylaxis.

Ossification

Subcutaneous ossification associated with CVI is a well-documented entity.[153] The subcutaneous ossification may occur even in the absence of venous ulcers. The presence of bone at the base of the ulcer may be a cause for non-healing.

Patients with paralysis due to traumatic myelopathy are at increased risk for development of heterotopic ossification of the periarticular soft tissues. It starts with soft tissue inflammation near the large joints and can mimic superficial thrombophlebitis.[154] The pathologic process might involve the muscles and it was previously referred to as myositis ossificans. Although subcutaneous ossification has not been previously reported in association with a reticulate eruption, such a case has been observed by the author.

Oxalosis

Oxalate is the salt form of oxalic acid. More than 90% is excreted by the kidney, with a small amount of excretion into the lower gut. Oxalate and calcium can combine to form calcium oxalate kidney stones. Calcium oxalate stones are the most common type of kidney stones.

Primary oxalosis is due to genetic abnormalities leading to an increased hepatic production of oxalate. Secondary oxalosis can be caused by over-consumption of oxalate in foods, or increased absorption of oxalate from the intestinal tract associated with ileal resection or intestinal disease.[155, 156]

Renal deposition of calcium oxalate crystals can cause renal failure that is followed by a rise in serum calcium oxalate levels and eventual deposition of these deposits in other tissues. Deposition of calcium oxalate crystals in small vessels of the dermis and subcutis can present with livedo racemosa and subsequently reticulate purpura and cutaneous ulceration.[156,157] When larger vessels are involved, the crystal deposition can result in end organ damage.[158]

Oxalosis affects multiple organs due to deposition of calcium oxalate crystals and can have a poor prognosis

if left untreated.[35] Differentiating between calciphylaxis and oxalosis can be done via a biopsy of an involved area demonstrating the reticulate pattern.[35] The vessel walls will contain strongly birefringent yellow-brown crystals as against calciphylaxis, which shows basophilic calcium salt deposits within vessel walls and in the interstitium.

Vascular Anomalies

Vascular anomalies (tumours and malformations) and in particular those with an arterial involvement can present with a segmental reticulate pattern. The hexagonal pattern with surrounding pallor signals an underlying arterial involvement that should be differentiated from the sharply demarcated borders of a lymphatic malformation.

Vascular Tumours

Vascular tumours only rarely present as a reticulated stain. An example of such tumours is telangiectatic infantile haemangioma which presents as a reticulated stain in association with soft tissue hypertrophy.[159] These present as flat or slightly elevated lesions exhibiting numerous dilated superficial vessels. Tufted angiomas and congenital haemangiomas may also appear mottled and reticulated. Retiform haemangioendothelioma does not have a reticulate clinical appearance and the 'retiform' description refers to the histological finding of arborising blood vessels arranged in a retiform pattern.

Vascular Malformations

Vascular malformations are structural abnormalities of the vasculature due to errors in morphogenesis. Simple malformations may involve the underlying arteries, veins, capillaries, lymphatics or any combination of these vessel types. Involvement of arteries, arterioles, arterial capillaries or the subcutaneous superficial venous network can result in a reticulate presentation.

Cutis Marmorata Telangiectatica Congenita

Cutis Marmorata Telangiectatica Congenita (CMTC), or van Lohuizen's Syndrome, is a complex congenital malformation composed predominantly of capillary and venous vessels. First described by the Dutch physician Van Lohuizen in 1922, it is characterised by a partly blanchable branched pattern of livedo racemosa that may resemble physiologic CM (Figures 22 and 39).[29] In contradistinction

with CM, the reticulate eruption is usually asymmetrical, localised, segmental and will not resolve completely with warming of the skin.[160,161] It can appear on the extremities, and less commonly, on the trunk or the face and can be generalised.[161] Pallor of the skin at the centre of the rings is often reported and the involved skin may become atrophic and may ulcerate. Ulceration is more likely when the involved skin overlies the elbows and knees. Telangiectasias and phlebectasias often accompany the livedo racemosa. The involved limb itself may be hypoplastic. The involved subcutaneous fat may also show signs of atrophy and induration. In some patients, there is fat hypertrophy.

The presence of atrophy and ulceration helps to differentiate CMTC from physiologic CM. CMTC should also be differentiated from persistent true CM that can be seen in Trisomy 21, Cornelia de Lange syndrome and homocystinuria. Aplasia cutis in association with CMTC should prompt exclusion of Adams-Oliver syndrome.

In the first weeks of life, the lesions of CMTC may appear less reticulated and look very similar to a capillary malformation. Unlike capillary malformations, CMTC has a tendency to fade with time in most patients and marked improvement is often noted in the first two years of life. Fading is rarely complete and may leave residual reticulate lesions.

CMTC has overlapping features and clinical similarities to the Klippel-Trenaunay and Sturge-Weber syndromes. These three entities form a group of vascular malformations associated with other developmental defects representing defects of the mesodermal system during embryonic life.[162]

Figure 39: *Livedo racemosa secondary to Cutis Marmorata Telangiectatica Congenita (Courtesy of Dr Orli Wargon)*

Adams-Oliver Syndrome

This is a rare disorder characterised by CMTC occurring in association with aplasia cutis congenita of the scalp, bony abnormalities of the limbs, cranial and cardiac malformations.[163] CMTC is an inconstant feature of the syndrome and may occur in up to 15% of patients.[164] When present, CMTC is usually generalised. Lower limb defects are common and of variable severity.[165]

Adams-Oliver syndrome may result from an early embryologic vascular abnormality. Autosomal dominant inheritance is most commonly reported but recessive inheritance is reported in some families. Parents may only demonstrate CMTC.

Phacomatosis Cesiomarmorata

Phacomatosis pigmentovascularis (PPV) is a group of conditions that present with a combination of pigmented as well as vascular malformations. The Greek term phakos means naevus and phakomatosis was originally used to refer to a group of conditions that had in common the presence of hamartomas involving the skin and/or eyes. Hence conditions such as Neurofibromatosis and Tuberous Sclerosis were classified as Phakomatoses. The Greek letter k was replaced with the Latin c and Phacomatosis is today mainly applied to genetically determined diseases characterised by the presence of two or more different naevi, such as phacomatosis pigmentovascularis or phacomatosis pigmentokeratotica.[166]

In 2005, the German Dermatologist, Rudolf Happle proposed a new classification which eliminated the cumbersome traditional numbering and lettering of these conditions.[166] Based on this new classification, the traditional type I does not exist, and the extremely rare traditional type IV is now included in the group of unclassifiable forms. The types IIa and IIb are now called phacomatosis cesioflammea (blue spots [caesius = bluish grey] and naevus flammeus); the types IIIa and IIIb are now called phacomatosis spilorosea (nevus spilus coexisting with a telangiectatic nevus), and type V is phacomatosis cesiomarmorata (blue spots and CMTC).

Phacomatosis cesiomarmorata is characterised by a coexistence of nevus ca (blue spot, aberrant Mongolian spot) and CMTC (Figure 40). Non-allelic twin spotting has been proposed as the possible aetiology.[167]

Macrocephaly-Capillary Malformation

This is a rare sporadic disorder that was previously named Macrocephaly-CMTC. This designation was a misnomer as the vascular anomaly seen in this condition is in fact a reticulated capillary malformation and not cutis marmorata or CMTC.[168]

This syndrome is characterised by a CMTC-like patchy reticulated capillary malformation occurring in association with macrocephalic neonatal hypotonia and developmental delay. Other associations include hydrocephalus, frontal bossing, joint hypermobility, and toe syndactyly.

The capillary malformation can be found on the nose and philtrum or scattered over the limbs and trunk. The lesions usually lack the cutaneous atrophy seen in typical CMTC. The skin lesions never ulcerate and can fade over time. These patients often have hemi-hypertrophy of a lower limb.

Genuine Diffuse Phlebectasias (Bockenheimer Syndrome)

Genuine diffuse phlebectasia of Bockenheimer may from time to time present with a pattern that might be interpreted as reticulate.[169] This condition is a deep venous malformation that is not detected at birth, but first noted in childhood. It is characterised by the gradual development of large multiple venous sinusoids. The lesions usually involve an extremity and are associated with a poor prognosis because of the frequent occurrence of thrombosis, bleeding, ulceration, infection, and gangrene.

Non-Vascular Reticulate Eruptions

A number of conditions without a primary vascular origin can present with a reticulate pattern (Table 2). The reticulate pattern in these conditions may be caused by pigment

Figure 40: *Phacomatosis cesiomarmorata*

deposition or an infiltrate. The pigmentation may arise in the dermis or epidermis and may be post-inflammatory. The infiltrate may be inflammatory or neoplastic.

A) Congenital Conditions

Reticulate Pigmented Anomaly (Dowling Degos Disease)

Dowling first described this genodermatosis in 1938.[170] It is an autosomal dominant disorder first appearing in mid-twenties characterised by pruritic reticulate hyperpigmentation of the flexures, dark comedo-like lesions on the back and neck, and pitted perioral acneiform scars.[171] Speckled dark macules may be seen on the genitalia and may be a cutaneous marker of underlying testicular carcinoma. Other associations include mental retardation, and epidermal or pilar cysts.[172] Galli-Galli disease is a rare genodermatosis in the spectrum of reticulate hyperpigmentation probably best regarded as an acantholytic variant of Dowling Degos Disease.

Reticulate Acropigmentation of Kitamura (RAK)

This condition, more commonly seen in Japanese, is characterised by atrophic, hyperpigmented macules on the dorsal aspects of the hands and feet. Lesions appear during childhood and darken with time.[172]

Reticulate Acropigmentation of Dohi (RAD)

RAD is characterised by the presence of hyperpigmented and hypopigmented pinpoint macules over the dorsa of the hands and feet and occasionally on the arms and legs. This is in contrast to RAK where hypopigmented macules are not observed.

Dyskeratosis Congenita

Dyskeratosis congenita was originally described by Zinsser in 1906.[173] This condition is a rare genodermatosis most commonly caused by an X-linked recessive mutation that affects the skin, mucous membranes, and nails. The triad of reticulated hyperpigmentation of the skin, a premalignant mucosal leukoplakia, and nail dystrophy defines this syndrome. The cutaneous presentation of dyskeratosis congenita involves reticulate hyperpigmentation of the neck, chest, and skin folds. Clinically and histologically, the skin eruption can mimic chronic GVHD.

Naegeli Franceschetti Jadassohn Syndrome (NFJS)

This syndrome was first described by Naegeli in 1927. It is a rare autosomal dominant form of ectodermal dysplasia characterised by a mild punctate palmoplantar hyperkeratosis and reticulate hyperpigmentation of the skin. The grey-brown pattern of reticulate pigmentation starts around the age of 2 affecting the abdomen, periocular and perioral regions. Involvement of the neck, trunk, proximal extremities, axillae, groin, and flexures is variable.[172] The main clinical feature of this condition is heat intolerance, flushing and reduced sweating, with a potential for dizziness and collapse after mild exercise due to the involvement of sweat glands. Characteristically, patients lack dermatoglyphics (fingerprint lines).

Dermatopathia Pigmentosa Reticularis (DPR)

DPR is a very rare disorder with the diagnostic triad of generalised reticulate hyperpigmentation, non-cicatricial alopecia, and onychodystrophy. The reticulate hyperpigmentation affects the trunk more than extremities.[172]

Figure 41: *Erythema ab igne (Courtesy of Dr Adrian Lim)*
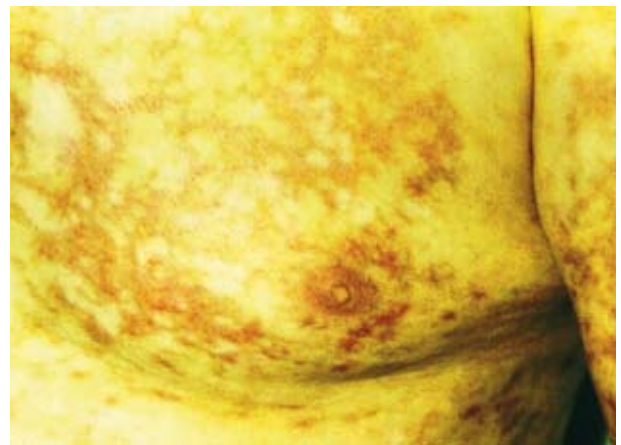
Figure 42: *Graft vs. host disease*

Partington Syndrome

This condition is a rare recessive X-linked syndrome characterised by a progressive reticulate pigmentation of the skin,[174] mental retardation, seizures, ataxia, dystonic movements of the hand, dysarthria, and an awkward gait.[175]

B) Acquired Conditions

Erythema ab igne (EAI)
[Latin: ab (from) + igne (fire)]

Erythema ab igne also known as heater dermatitis or toasted skin syndrome, is due to repeated exposure of skin to heat. It presents with reticulate erythema and pigmentation in areas of chronic heat exposure (Figure 41). The pigment is primarily melanin and it represents a post-inflammatory hyperpigmentation due to excessive exposure of the superficial venous plexus to infrared radiation.

The eruption begins as a mild transient reticulate erythema but over months of continued infrared exposure, the erythema becomes fixed and persistent and evolves into pigmentation. Later in the course, the affected skin becomes widely atrophic and hyperpigmented and only the borders will show a reticulate pattern.

Once the infrared exposure is ceased, pigmentation may resolve within several months. There is a possible association with squamous cell carcinoma that may arise in areas affected by EAI.

The histology usually includes a mild superficial perivascular predominantly lymphocytic infiltrate and prominent pigment incontinence. Telangiectasis within the papillary dermis and occasional haemosiderin may be seen more commonly on the legs.

Confluent and Reticulated Papillomatosis

Also known as Gougerot Carteaud Syndrome (GCS), this condition was first described in 1927.[176] It presents with small brown hyperkeratotic papules and patches that become confluent centrally and reticulated at the periphery. The first lesions usually appear in the intermammary area and possibly the mid-back but subsequent lesions may develop on the neck, axillae, and upper abdomen.

GCS is more common in women and people with darker skin. Although usually sporadic, there have been reports of familial involvement.[177] GCS has been found in association with amyloidosis and endocrine abnormalities, such as

Figure 43: *Cutaneous T-cell lymphoma (Mycosis Fungoides) presenting as a reticulate eruption. Note the stellate inflammatory erosions.*

Figure 44: *Child with Zinc deficiency presenting with a reticulate eruption (Courtesy of Dr Adrian Lim and Dr Orli Wargon)*

diabetes mellitus and thyroid disease.[172] An abnormal tissue reaction to *Pityrosporum orbiculare* has been suggested as the aetiology and some cases of GCS have responded to either systemic and even topical antifungal therapy.

Reticular Erythematous Mucinosis (REM)

This is another reticulated eruption that may also appear on the mid chest area. REM occurs more commonly in females. It presents with erythematous macules or papules in a reticulate distribution exacerbated by exposure to sunlight. The eruption is usually localised to the midline of the chest and back but may spread to the lower abdomen. Histologically, there is a mononuclear cell infiltrate and deposits of mucin in the dermis.[178] REM is associated with systematic diseases and in particular with autoimmune disorders.[179] SLE has been reported to present with REM.[180]

Graft vs. Host Disease (GVHD)

GVHD is seen following haematopoietic stem cell transplantation using peripheral blood, cord blood, or bone marrow transplantation.[181,182] Dermatological manifestations have been reported in up to 79% of transplant patients and contribute to morbidity. A lichen planus type cutaneous eruption in a reticulated pattern is one of the manifestations of acute GVHD (Figure 42).[182]

Other Conditions

Neonatal lupus erythematosus and Langerhans cell histiocytosis can both present with a reticulate pattern of the inflammatory infiltrate.[183] Porphyria cutanea tarda can present with reticulate hyperpigmentation in a melasma-like pattern.[184] Macular amyloidosis typically affects the upper back and limbs and can present with brownish macules distributed in a reticulate, rippled pattern.[185] Oral lichen planus presents with a reticulate slightly raised, white keratotic mucosal streaks, termed Wickham's striae. Parapsoriasis and Mycosis Fungoides (MF) may rarely present in a reticulate pattern (Figure 43). MF with a fatal outcome has been reported to present with a reticular pattern on the chest mimicking REM.[186] Metabolic disorders and zinc deficiency can present with a reticulate eruption (Figure 44).

Acknowledgements

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