REVIEW

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Obliterative foam-cell arteriopathy. A unifying concept embracing several entities previously described as radiation, decidual, transplant, and intratumoral-associated arteriopathy

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Abstract

This review article aimed to postulate the existence of a specific arterial injury having as its histological hallmark a collection of macrophages loaded with lipids in the intima of small-sized and medium-sized arteries causing narrowing or complete obstruction. The proposal is made that a series of previously described entities, such as ionizing radiation arteriopathy, acute atherosis (foam-cell decidual arteriopathy), transplant chronic arteriopathy of solid organ allografts, and intratumoral-associated foam-cell arteriopathy constitute different manifestations of the same basic morphological process identified as obliterative foam-cell arteriopathy (OFCA). OFCA is a local (single-organ) lesion in the aforementioned diverse processes with variable etiopathogenesis but converges in a single morphological marker. This arteriopathy is essentially an intimal disease. The processes in which the OFCA appears are known under a variety of names partly dependent on the location of the lesion. The basic unifying mechanism of the different entities is endothelial activation and dysfunction (local arterial endotheliopathy), preferably in small-sized or medium-sized arteries (100 to 500 μm in external diameter).

Keywords: foam-cell arteriopathy, foam-cell vasculopathy, radiation arteriopathy, decidual arteriopathy, transplant arteriopathy, intratumoral arteriopathy.

Introduction

This review aimed to describe and illustrate the morphology of a special form of vascular injury in human tissues in various clinical situations for the surgical pathologist. Vascular alterations occur in a repetitive form in diverse organs and respond to different etiopathogenesis.

Obliterative foam-cell arteriopathy (OFCA) can be morphologically defined as localized (isolated) vasculopathy limited to small-sized or medium-sized arteries (100 to 500 μm in external diameter) characterized by accumulation of lipid-laden macrophages in the intima causing narrowing or complete obstruction. The accumulation of foam cells in the intima can be eccentric or concentric and the muscular arterial wall may show fibrinoid necrosis and/or hyalinization depending on its evolutionary period. An adventitial cuff of fibrous tissue and mononuclear cell infiltration can also be observed (Figure 1).

This arteriopathy has been reported in a variety of clinical environments including (*i*) ionizing radiation arteriopathy; (*ii*) acute atherosis (foam-cell decidual arteriopathy); (*iii*) transplant chronic arteriopathy of solid organ allografts; and (*iv*) intratumoral foam-cell occlusive arteriopathy.

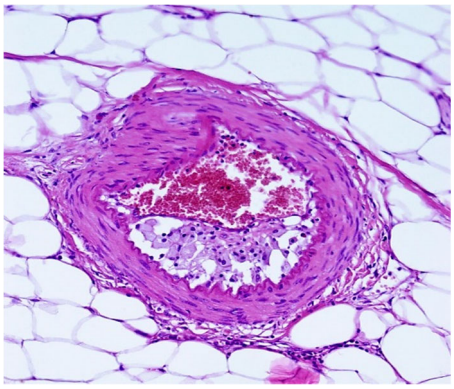

Figure 1 – ***OFCA is characterized by the accumulation of lipid-laden macrophages in the intima causing narrowing. A thin adventitial cuff of fibrous tissue and mononuclear cell infiltration is present. HE staining, ×200. HE: Hematoxylin–Eosin; OFCA: Obliterative foam-cell arteriopathy.***

Clinical settings of the obliterative foam-cell arteriopathy

The obliterative foam-cell arteriopathy of the ionizing radiation

This arteriopathy was observed by Sheehan [1], in 1944, in eight samples from patients with adenocarcinomas of the rectum and uterus treated with radiation. Martin *et al.* [2] rediscovered the lesion in 1957, in 14 uteri treated with radiation for malignant epithelial tumors. Kirkpatrick [3] reproduced this arteriopathy experimentally, in 1967, by irradiating the ears of hyperlipidemic New Zealand rabbits.

The lesion was also reproduced in rabbits without hyperlipidemia [3]. Ackerman [4] considered the OFCA to be a specific finding of radiation effect on human vessels. The delayed or chronic phase of radiation injury begins to develop after a period of six months to three years post-treatment but may occur up to 30 years following treatment [5]. OFCA is most frequently seen in the alimentary tract (from the oral cavity to the rectum) from which the surgical pathologist receives most surgical specimens with radiation injury [6–8]. Vascular lesions similar to those described in the alimentary tract are seen in the fibrous pancreas after radiation [7]. The female genital tract is also frequently affected following radiation since combined preoperative radiation and surgical removal is an appropriate therapy for some uterine neoplasms [7]. On the other hand, extensive areas of normal brain tissue can be irradiated when adjacent tissues, such as paranasal sinuses, nasopharynx, orbit, ear, parotid, and cervical lymph nodes are treated by radiation. In these situations, an extremely serious multifocal OFCA is produced [9]. However, the most frequent manifestation of radiation-induced brain damage is intracranial OFCA after radiation therapy for brain tumors [10, 11].

The OFCA following radiation shows more often eccentric foam cell accumulation in the intima [1, 12, 13] (Figure 2). Nevertheless, a concentric accumulation of foam cells can be seen as observed in Figure 3. In some arteries, red cells and foam cells are mixed in varying proportions (Figure 4), but foam cells often occur alone. Additionally, cholesterol crystals may be observed [1]. Some arteries show intimal fibrosis. This intimal fibrosis is not specific to radiation, but it is more common than the characteristic foamy plaque (Figure 5). Depending on the time elapsed, the media may show fibrinoid necrosis (Figure 6) or thickening with a hyaline appearance [1, 12] (Figure 7). Endothelial cells (ECs) have high radiation sensitivity showing swelling and enlarged prominent nuclei. Thrombosis may occur rarely. Delayed alterations accompanying OFCA include atrophy in lining epithelia (skin, respiratory, alimentary, and urinary tracts) as well in glands (cutaneous, mammary, salivary, pancreatic, and prostate glands), and parenchymatous tissues (lung, kidney, gonads) [13]. Metaplasia can be seen in some organs. Thus, squamous metaplasia is commonly observed in the prostate [13]. Atypia of the epithelial cells can affect the nucleus and cytoplasm. Chromatin is usually smudged, and nucleoli are prominent (owl's eye nucleoli) [14]. Differential diagnosis should be made between radio-induced atypia of non-tumor epithelium and residual neoplasia [13]. Stromal lesions include interstitial edema, fibrinous exudate, fibrosis that tends to be patchy and multifocal (Figure 8), atypical fibroblasts (swallow-tail cells), and asymmetrical, dilated (telangiectatic) blood capillaries (Figure 9) with enlarged endothelial nuclei [12, 13]. Fibrin is deposited in the interstitial tissues and on the serosal surfaces, such as the pleura and pericardium [13].

It should be noted that the OFCA is not a pathognomonic feature of injury produced by ionizing radiation. Nonetheless, the association with the delayed alterations accompanying OFCA included above is sufficiently characteristic for its recognition.

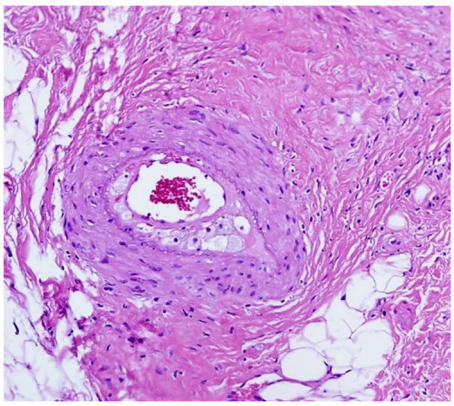

Figure 2 – ***Eccentric plaque-like thickening of the intima-containing foam cells (rectum). HE staining, ×200.***

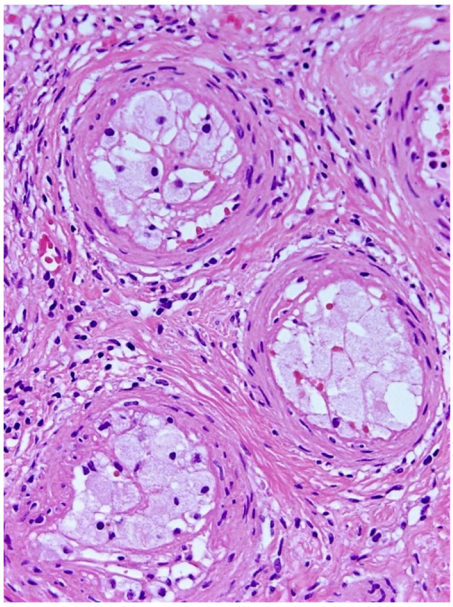

Figure 3 – ***Concentric thickenings of the intima of small arteries containing foam cells (ovary). HE staining, ×400.***

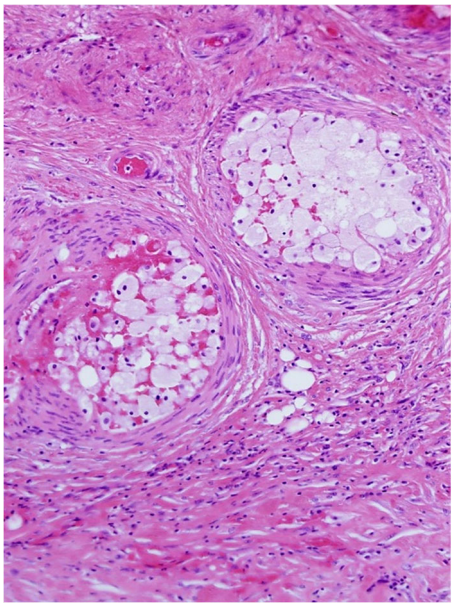

Figure 4 – ***In some arteries, red cells, and foam cells are mixed in varying proportions (rectum). HE staining, ×200.***

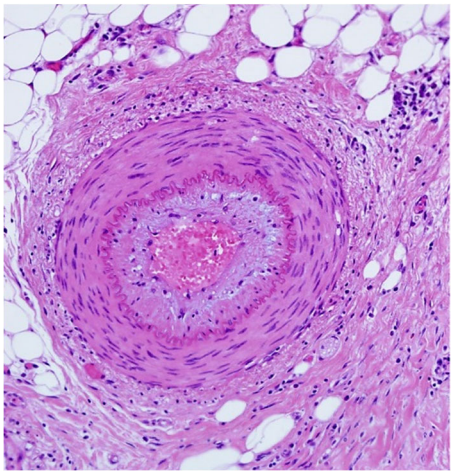

Figure 5 – ***Fibrosis of the arterial intima with stenosis of the lumen (rectum). HE staining, ×200.***

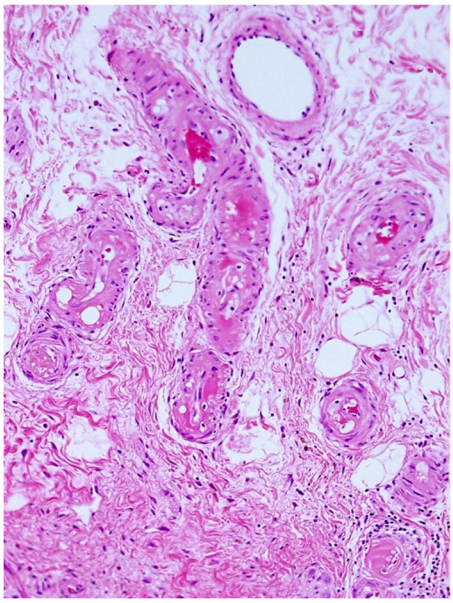

Figure 6 – ***Fibrin (fibrinoid necrosis) is present in the arterial wall (rectum). HE staining, ×400.***

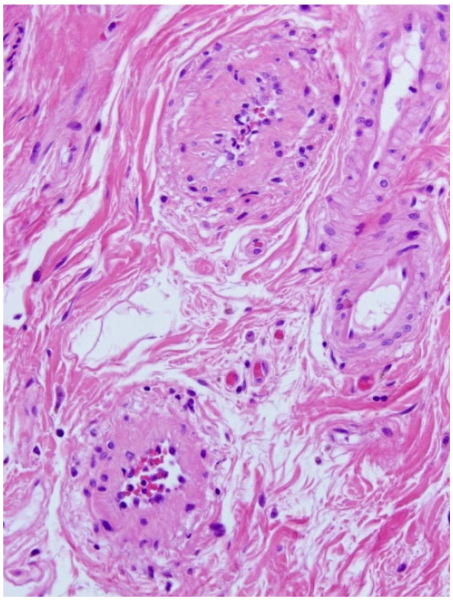

Figure 7 – ***Hyalinosis of the arterial wall (rectum). HE staining, ×400.***

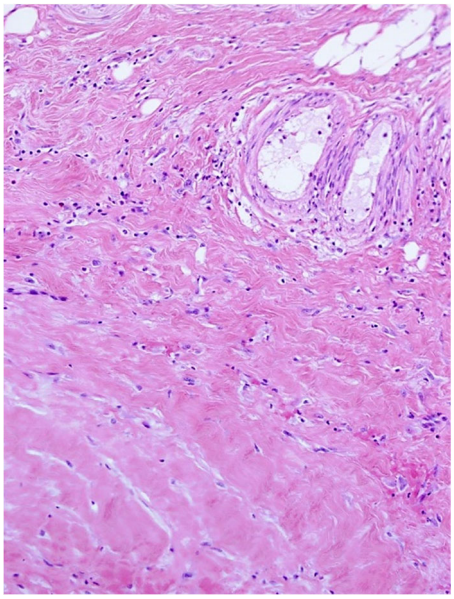

Figure 8 – ***Rectal submucosal fibrosis. HE staining, ×200.***

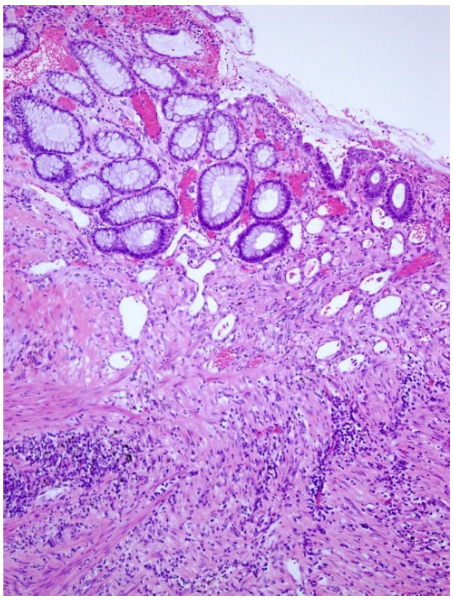

Figure 9 – ***Dilated blood capillaries of the rectum. HE staining, ×100.***

The cause of OFCA, according to Sheehan [1], is the migration of monocytes from the bloodstream into the intima and their subsequent transformation into foam cells by their ingestion of lipids. These lipids are released by the breakdown of red cells after passage across the endothelium made more permeable than usual by irradiation. In favor of this interpretation, fine granules of hemosiderin can be seen in some intimal foamy macrophages (Figure 10). Microvascular ECs are especially sensitive to ionizing radiation [14]. According to Wijerathne *et al.* [15], ionizing radiation induces EC damage through deoxyribonucleic acid (DNA) damage, inflammatory activation, an increase of permeability, expression of cytokines, such as interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), and adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin, and P-selectin, endothelium–neutrophil interaction,

releases of oxygen radicals (reactive oxygen species, ROS) and proteases, mitochondrial damage and EC apoptosis. Enhanced leukocyte–EC interactions increase the barrier permeability and initiate apoptotic pathways, which are important radiation-induced inflammatory responses in the pathology of diverse organs. The hyperpermeability of injured arteries promotes the extravasation of fibrinogen into the vessel wall and extravascular space, which transforms into fibrin. Activation of TGF-β induces the deposition of collagen in the fibrin with the onset of fibrosis [15]. Foamy macrophages are the result of EC hyperpermeability.

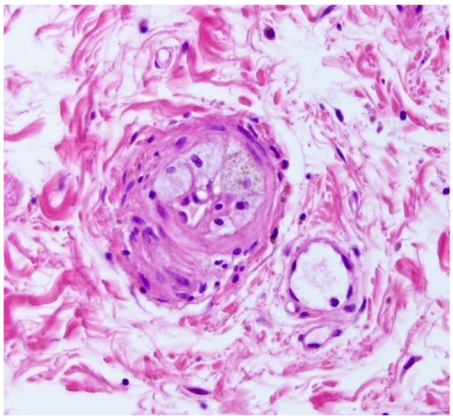

Figure 10 – ***Foamy macrophages show fine granules of hemosiderin in their cytoplasm (rectum). HE staining, ×400.***

Acute atherosis (atherosis of macrophage type; foam-cell decidual arteriopathy)

In 1945, Hertig [16] first described the hypertensive albuminuric toxemia of pregnancy or more specifically pre-eclampsia and eclampsia as "acute degenerative arteriolitis". Preeclampsia has been described as pregnancy-related new-onset hypertension and proteinuria. It may progress into a more serious form of the disease, known as HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelet count) syndrome or eclampsia. That lesion in its early period appears as an accumulation of foamy, lipid-rich mononuclear phagocytes within the intima of the spiral arterioles of the placental bed. This stage is quickly followed by a fibrinoid degeneration of the media, which is followed by a fibroblastic proliferation of the intima, which causes partial or total obliteration of the lumen. The term acute atheroma/atheromatosis to designate the arterial lesion was introduced by Sexton *et al.* [17]. Later, Zeek & Assali [18] named the vessel lesion acute atherosis. According to Sexton *et al.* [17], this lesion could be observed in women with essential hypertension or chronic glomerulonephritis who also have preeclampsia or eclampsia. However, Zeek & Assali [18] regarded the acute atherosis of decidual spiral arterioles as being confined to patients with preeclampsia and true infarcts of the placenta. They observed that acute atherosis was the most common cause of obstruction producing these infarcts.

Acute atherosis is a vascular alteration in the placenta linked to poor placentation. For a pregnancy to be successful, the uterine spiral arteries must develop normally during the early stages of pregnancy. The spiral arteries physiologically evolve into dilated vessels with significant vessel wall structural alterations. They exhibit trophoblast invasion into the vessel wall, lumen dilatation, and replacement of the muscle wall with fibrinoid material. These changes strengthen the maternal blood supply to the placenta's intervillous space, providing sufficient nutrition and oxygen from the mother to the fetus. The first three months of pregnancy are critical in this process. Poor placentation is defined as a failure of the normal metamorphosis of spiral arteries [19]. Acute atherosis is very uncommon in a normal pregnancy but is more commonly observed in abnormal pregnancies including preeclampsia, spontaneous preterm labor, small for gestational age newborn, infant death, mid-trimester spontaneous miscarriage, placental abruption, preterm rupture of membranes and eclampsia [20]. Furthermore, some patients with diffuse scleroderma, idiopathic thrombocytopenic purpura, and systemic lupus erythematosus have decidual vessels with acute atherosis [21]. Acute atherosis is a focal lesion not affecting all spiral arteries. Thus, Stevens *et al.* [22] observed that the total number of arteries with acute atherosis is related to worse clinical outcomes and increased placental pathology.

De Wolf *et al.* [23] described the ultrastructure of acute atherosis in hypertensive pregnancy. The lesion in its early stage is characterized by endothelial injury, insudation of plasma into the vessel wall, myointimal cellular growth, and medial fibrinoid necrosis. Plasmatic lipids are engulfed by macrophages that are transformed into lipid-laden cells. The hallmark of acute atherosis is intimal lipid-filled foam cells, fibrinoid necrosis of the vascular wall, and periarterial lymphocytic infiltration in non-transformed uterine spiral arteries [19]. However, periarterial infiltrates are not systematically present around all acute atherosis lesions. On the other hand, it should be said that historically, a variation in acute atherosis definitions has been observed [24]. Thus, after analyzing 237 *decidua basalis* samples, Alnaes-Katjavivi *et al.* found that greater fibrinous deposits and perivascular leukocyte infiltrates were not necessarily associated with foam-cell accumulations [25]. These authors proposed an evidence-based research definition of acute atherosis. Thus, acute atherosis should be diagnosed exclusively by the presence of foam-cell lesions, defined as two or more contiguous, intramural, lipid-laden cluster of differentiation (CD)68+ cells [24, 25]. This simplified criterium has been reproducible by different investigators but may not be applied to myometrial or *decidua parietalis* arteries [25]. A protocol for diagnostic criteria for placental lesions including acute atherosis was published by Khong *et al.* [26]. It is important to indicate if the lesion is in the membrane roll, basal plate, or both [26]. Zhang & Baergen [27] have classified atherosis as atherosis of macrophage type (Zeek & Assali acute atherosis) and atherosis of (endovascular) trophoblast type. The marker for atherosis of macrophage type is CD68. Trophoblasts can show foamy changes. Foamy trophoblasts are recognized in atherosis because they show basophilic cytoplasm and positivity for CD56 [27]. Atherosis of the trophoblast type is associated with lower placental weight but not with other specific clinical features, such as preeclampsia or hypertensive disorders of pregnancy [27]. Figure 11 shows acute atherosis in the basal plate of a placenta from a woman with preeclampsia delivered at 36 weeks for falling fetal growth.

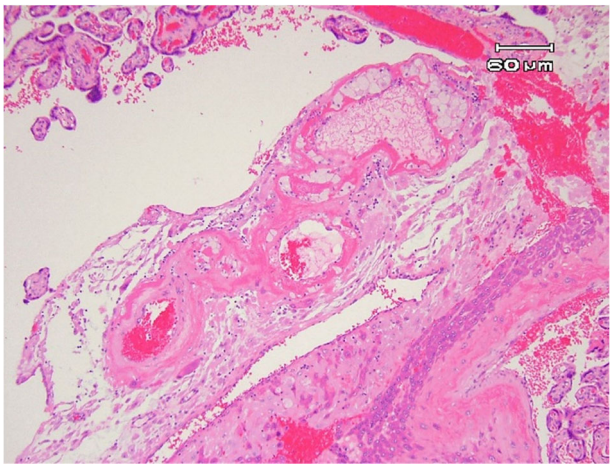

Figure 11 – ***Acute atherosis of the placenta. Collection of foamy, fat-laden mononuclear phagocytes in the intima and fibrinoid degeneration in the wall. Scanty perivascular lymphocytic infiltrate is present. HE staining, ×40. The image is courtesy of Dr. T. Yee Khong.***

The causes of acute atherosis are not completely established. Preeclampsia and eclampsia have been labeled as the "disease of theories". Decidual inflammation, immunological mechanisms, and endothelial shear stress can contribute to the development of the lesion [28]. Recently, an association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection severity and subsequent development of preeclampsia has been established: the more severe coronavirus disease 2019 (COVID-19), the greater the risk of preeclampsia [29]. However, the most widely recognized theory is that poor uteroplacental vascular remodeling causes decreased placental blood flow, which leads to placental ischemia/hypoxia. Angiotensin II type 1 receptor autoantibody (AT1-AA), vascular endothelial growth factor receptor-1 (VEGFR-1), and cytokines like TNF-α and IL-6 are all produced by the ischemic placenta and cause maternal endothelial dysfunction, which is characterized by increased circulating endothelin-1, ROS, and increased vascular sensitivity to angiotensin II. These elements combine to impair kidney function and increase blood pressure during pregnancy [30]. Endothelial stress induces increased permeability with the penetration of fibrin and the formation of foam cells [29]. Lendrum [31–33] considered acute vessel wall fibrin deposit as a manifestation of locally increased permeability or "plasmatic (fibrinous) vasculosis". Therefore, during pregnancy, there is a connection between placental ischemia, endothelial dysfunction, and hypertension. On the other hand, there is increasing concern about the idea that women having a history of preeclampsia may be more susceptible to developing cardiovascular disease in the future if their placenta has acute atherosis [19].

Transplant chronic arteriopathy of solid organ allografts

The obliterative chronic transplant arteriopathy (OCTA) is a complex process that has a substantial impact on long-term graft and patient survival after solid-organ transplantation. OCTA is characterized by occlusive narrowing of the arteries of the allograft causing the transplant to undergo fibrotic and anoxic alterations. This arteriopathy is the most common long-term cause of death and re-transplantation in heart transplant recipients [34] and other solid organ allografts.

OCTA is a vascular remodeling involving the injury and apoptosis of ECs, which ensues smooth cell migration and proliferation causing intimal thickening and allograft artery blockage. The histopathology of vascular reorganization is identified by concentric fibromuscular hyperplasia of the intima together with luminal constriction often accompanied by lymphocyte infiltrates (mostly CD4+ T-lymphocytes) and macrophages. In addition, there are a variable number of foamy cells [35–39]. An adventitial cuff of fibrous tissue with or without mononuclear inflammatory infiltrates can be observed. Figure 12 shows the complete obliteration of one arterial intima with the presence of concentric foam cells and fibrin accumulation in a pancreatic transplant. In the cardiac transplant, the large epicardial, small epicardial, and intramyocardial branches of allograft chronic vasculopathy are affected, However, in small epicardial and intramyocardial branches, foam cells usually are not prominent [40]. The luminal occlusion of large and small epicardial coronary arteries and smaller intramyocardial arteries leads to a spectrum of diseases ranging from cardiac failure, myocardial ischemia, infarction, and death. Excellent images of concentric intimal accumulation of abundant foam cells have been published in chronic renal and hepatic vascular rejection [38, 39].

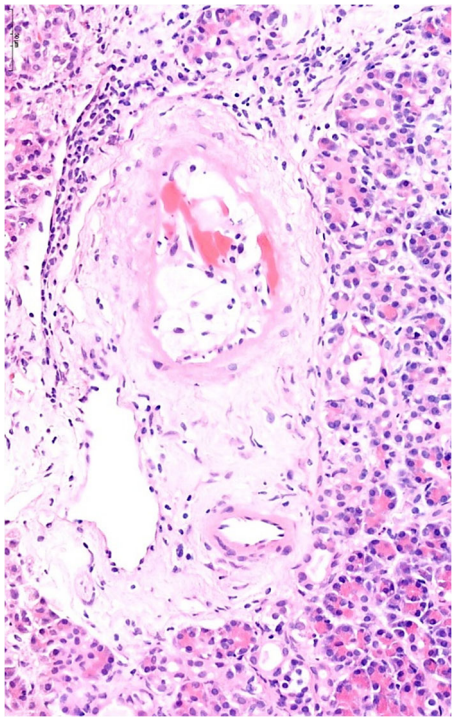

Figure 12 – ***Chronic vascular pancreatic allograft rejection. Total luminal obliteration by foamy cells and fibrin deposit in the intima. HE staining, ×330.***

The OCTA lesions are distinct from those seen in atherosclerosis. OCTA lesions do not result in atheroma development or calcification. They are concentric and diffusely involve both epicardial coronary arteries and intramyocardial branches. On the other hand, atherosclerotic plaques are eccentric, frequently calcified, and impact proximal vessels, and spare intramyocardial branches. In addition, inflammation is restricted to the intima and is not conspicuous [35].

Leukocytes, macrophages, and platelets are involved in the development of OCTA. These mediators release cytokines that cause inflammation, increased cell extravasation, EC activation, and the production of proinflammatory molecules in the endothelium. The recognition of foreign major histocompatibility complex (MHC) class II antigens on the surface of the graft endothelium by host CD4+ T-lymphocytes, which secrete cytokines like interferon-gamma (IFN-γ) and TNF-α to activate adhesion molecules, mediates chronic rejection. Smooth muscle cells exhibit intimal proliferation in response to the production of growth factors and vasoactive peptides by endothelial and inflammatory cells [41]. In the intimal space, there is an accumulation of cells corresponding to foamy macrophages [42], smooth muscle lipid-laden cells [40], and T-lymphocytes. Besides, there is an increase in extracellular matrix (ECM) proteins and fibrosis produced by smooth muscle cells [43]. The cellular accumulation and fibrosis obliterate the lumen leading to anoxic and fibrotic changes in the renal allograft [41] or ductopenia in the hepatic allograft [44]. The accumulated cells in the enlarged arterial intima are derived from the recipient [45].

OCTA is mainly a disease of the arterial intima [46]. Labarrere [21] considered chronic vascular rejection in solid allografts an acute atherosis-like lesion. Endothelial injury is central to the pathophysiological mechanisms underlying solid organ allograft vasculopathy [47]. OCTA is considered pathognomonic of allograft chronic rejection [48].

Intratumoral foam-cell occlusive arteriopathy

Isolated (localized) primary vasculopathy/vasculitis limited to a specific anatomic site or solitary organ is very uncommon. A crucial issue is whether single-organ vasculitis is really an isolated form of disease or a precursor to systemic vasculitis. Isolated vasculitis should be classified in two ways: (*i*) by the organ involved and (*ii*) by the histological type [49]. Single-organ vasculitis has been reported in the gastrointestinal and genitourinary tracts, breast, aorta, coronary arteries, skin, lung, retina, peripheral nervous, and central nervous systems [49–52].

A rare form of isolated vasculitis can be present exclusively within a neoplasm. The types described include localized fibrinoid vasculitis in renal angiomyolipoma and granulomatous (giant cell) vasculitis in intramuscular lipoma [53, 54]. Tumor-associated foam-cell occlusive arteriopathy is also a very uncommon form of intratumoral vasculopathy (Figure 13). To our knowledge, this entity has only been reported three times [55–57]. A review of the literature is presented in Table 1. All cases occurred in women (mean 58.7 years; range 49–61 years) with mesenchymal tumors, one of which was a benign uterine leiomyoma. All tumors showed signs of ischemia attributable to vascular obstruction (Figure 14). Only one patient presented hypercholesterolemia. The vasculopathy was limited to the tumor tissue and did not present extra neoplastic extension. In Case No. 2, there were scattered lymphocytic infiltrates involving and encircling the walls of small vessels (Figure 15). Lymphocytes were also seen in the subendothelial space and among the ECs constituting figures of intimitis (Figure 16) and endothelialitis. Most of the lymphocytic infiltration was made up of CD3+ cells, with a higher proportion of CD4+ cells and fewer CD8+ cells. Few CD20+ cells were seen. The lesion was interpreted as (idiopathic) lymphocytic vasculitis [58, 59].

Table 1 – ***Intratumoral OFCA. Review of the literature***

Case No./ [Reference]	Age [years]/ Sex	Location and tumor type	Tumor lesions	Clinical treatment	Hypercholesterolemia	Associated lymphocytic vasculitis
1/[55]	61/F	Cerebral and leptomeningeal Hodgkin lymphoma	Infarction Hemorrhage Vascular thrombosis	Acyclovir Ganciclovir Antimicrobial	Not reported	No
2/[56]	66/F	Gastric Gastrointestinal stromal tumor	Rarefaction Hydropic swelling Microcysts Vascular thrombosis	None	Present	Yes
3/[57]	49/F	Uterine leiomyoma	Edema Infarct-type necrosis Vascular thrombosis	Tranexamic acid	Not reported	No

F: Female; OFCA: Obliterative foam-cell arteriopathy.

The precise mechanism of intratumoral foam-cell occlusive arteriopathy histogenesis in Cases Nos. 1 and 2 is unknown. It has been established that the kind of tumor vasculature is determined by the tumor phenotype. Just as there are multiple cellular phenotypes in any tumor, so there may be multiple EC phenotypes in the neoplastic microenvironment [60]. Within the context of a tumor, cytogenetic changes can be acquired by tumor endothelial cells (TECs). They may thus be morphologically and functionally diverse, aneuploid, unstable, exhibit aberrant centrosomes, not undergo senescence, and resist apoptotic triggers. Furthermore, tumor malignant cells can transdifferentiate into TECs [61]. We can speculate that this situation may provoke an immune response. Thus, aberrant endothelium cells can be identified by circulating T-lymphocytes. TECs are adhered to by activated T-lymphocytes, which also permeate the vascular wall and promote monocyte and lymphocyte cell adhesion as well as their interactions with IL-1, TNF-α, lymphotoxin, and IFN-γ. Endothelial damage and oxidative stress result from this. Foamy macrophages may appear because of lipid insudation into the intima. Hypertension can contribute to endothelial dysfunction by producing monocyte chemoattractant protein-1 (MCP-1) and other chemokines that elicit the blood vessel inflammatory response [62].

In Case No. 3, the authors [57] explained that leiomyomas show a structurally and functionally aberrant vascularization with low vascular density and increased plasminogen activator inhibitor-1 (PAI-1) expression. They proposed that this situation predisposes leiomyomas to increased susceptibility to ischemia and impaired fibrinolysis with uncontrolled fibrin deposition. They suggested that Tranexamic acid and the tumor microenvironment acting in combination contributed to intratumoral foam-cell occlusive arteriopathy.

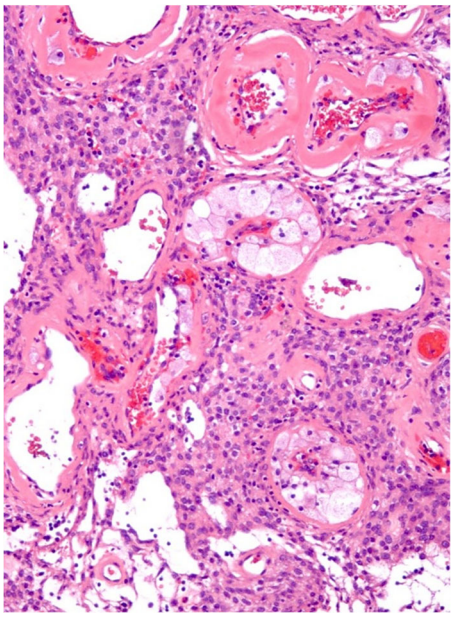

Figure 13 – ***Intratumoral associated foam-cell arteriopathy. Vessels of varying sizes show subendothelial foam cell infiltration, luminal narrowing, occlusion, and hyalinization of their walls. HE staining, ×100.***

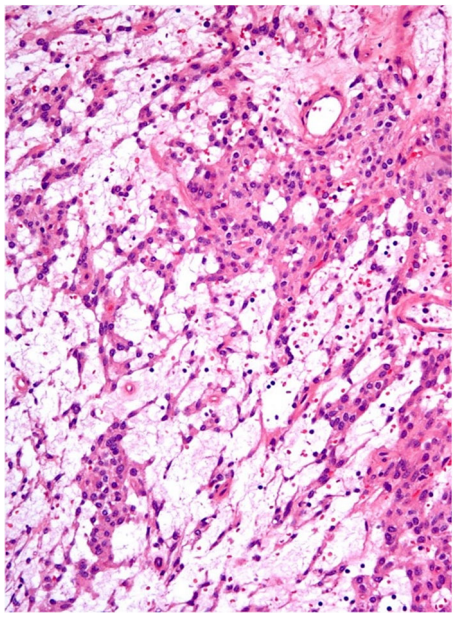

Figure 14 – ***GIST showing ischemia signs: hydropic swelling and extensive formation of microcysts of the cells. HE staining, ×100. GIST: Gastrointestinal stromal tumor.***

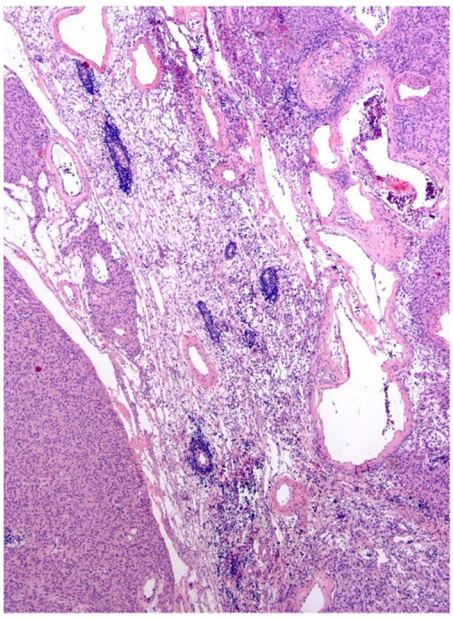

Figure 15 – ***Intratumoral associated lymphocytic vasculitis in a GIST. The lymphocytic infiltrate involves and surrounds the walls of small vessels. HE staining, ×25.***

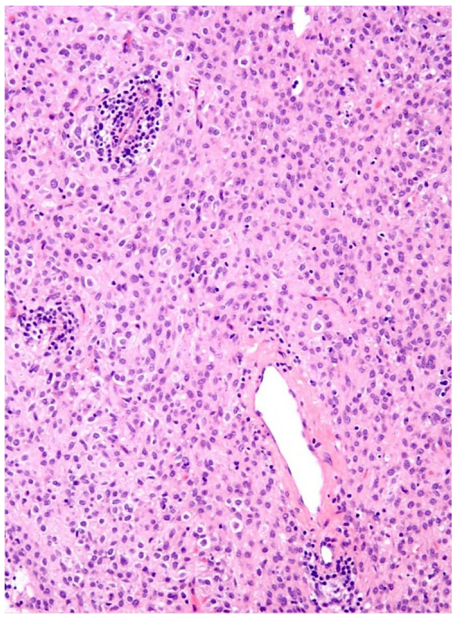

Figure 16 – ***Lymphocytic vasculitis in a GIST: intimitis and transmural lymphocytic infiltrate. HE staining, ×100.***

Discussions

It is evident that patients with different clinical conditions show the same obliterative arterial lesion with the presence of intimal foam cells. We suggest that the link between these conditions is endothelial activation and endothelial dysfunction in local arteries (local arterial endotheliopathy).

A single layer of ECs lines all blood vessels. ECs are an interface between the bloodstream and the *tunica intima* of the arterial wall. These cells act as a selectively permeable barrier regulating the delivery of oxygen, nutrients, and cellular components to the arterial wall and evacuating carbon dioxide and waste products. The transport of molecules between the bloodstream and *tunica intima* is carried out through cell–cell junctions and vesicular transport [63]. ECs share a common set of tasks, including hemostasis management, vascular permeability maintenance, mediation of both acute and chronic immune responses to various forms of injury, vascular tone regulation, and neoangiogenesis. These vital functions are controlled by multiple molecular pathways. The nitric oxide (NO) signaling pathway is one of the most significant. NO is a tiny, soluble gas that is essential for maintaining vascular homeostasis because of its potent vasodilatory, anti-inflammatory, and antioxidant characteristics [64].

Endothelial activation is characterized by the expression of cell-surface adhesion molecules, which are cytokines

released by inflammatory tissues and necessary for the recruitment and attachment of inflammatory cells. It also involves the endothelium being procoagulant and pro-inflammatory [65].

Increased chemokine release, leukocyte adherence, increased cell permeability, up-regulation of adhesion molecules, and ROS generation are all associated with endothelial dysfunction. ROS plays a role in vascular smooth muscle cell (VSMC) migration and proliferation, cytokine generation, and platelet activation. The main reason for endothelial dysfunction and subsequent vascular damage is an imbalance between the production of reactive ROS and antioxidant defense systems. The term endothelial dysfunction also refers to the reduced NO synthesis, which controls blood vessel dilation, and an imbalance in the contribution of chemicals that relax and contract the endothelium [63, 65, 66].

When monocytes cross the endothelium, they differentiate into macrophages. Macrophages control lipid metabolism through cholesterol uptake, esterification, and efflux. Proinflammatory stimuli downregulate the expression of cholesterol transporters resulting in the deposition of free and esterified cholesterol in macrophages and the production of foam cells. These cells can also originate from VSMCs and even from ECs [67]. VSMCs are the main source of ECM [67].

It can be postulated that compromised endothelial function (local arterial endotheliopathy) [68, 69] contributes to the pathogenesis of ionizing radiation arteriopathy, acute atherosis (foam-cell decidual arteriopathy), transplant chronic arteriopathy of solid organ allografts, and intratumoral foam-cell occlusive arteriopathy.

Conclusions

OFCA is morphologically defined as a localized (single-organ) form of vasculopathy limited to small-sized or medium-sized arteries characterized by accumulation of lipid-laden macrophages in the intima causing narrowing or complete obstruction. OFCA is mainly a disease of the arterial intima. We propose to group a series of previously described entities, such as ionizing radiation arteriopathy, acute atherosis (foam-cell decidual arteriopathy), transplant arteriopathy of solid organ allografts, and intratumoral-associated foam-cell arteriopathy that constitute different manifestations of the same basic morphological process identified as OFCA. The basic mechanism of development of this arteriopathy is endothelial activation and dysfunction (local arterial endotheliopathy).

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Compliance with ethical standards

This research is exempt from approval by the Ethics Committee of our institution because it is a conceptual study based on retrospective data.

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Declaration of competing interest

The authors declare that they have no conflict of interests.

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