Pfeifer-Weber-Christian Disease and Benign Multiple Subcutaneous Noninfiltrative Angiolipomas: A Puzzling Case and Review of a Rare Entitety

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Case report

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Abstract

Background: Pfeifer-Weber-Christian disease (PWCD) is one of many rare diseases that may be easily missed if there is not a high degree of suspicion. Angiolipomas are rare, benign subcutaneous tumors, composed of adipose tissue and blood vessels and often containing fibrin thrombi. The majority of angiolipomas occur sporadically; however, there is a minority of cases that have been associated with long-term corticosteroid use.

Case presentation: We report here an unusual case of PWCD associated with benign multiple subcutaneous noninfiltrative angiolipomas confirmed by skin biopsy. Systemic corticosteroid therapy was not effective at reducing flares of panniculitis, and during this therapy angiolipomas gradually increased in size. In contrast, administration of oral Cyclosporine A (CyA) led to a rapid remission of the PWCD.

Conclusions: As PWCD has no known aetiology and no specific treatment has been established, the successful therapy with the CyA supports the hypothesis that PWCD is a T cell mediated autoinflammatory condition. Also, this case represent very rare side effects of corticosteroid therapy, such as induction of de novo angiolipomas or increased growth of existing tumours. This case bring diagnostic difficulties in everyday clinical practice, especially in patients with panniculitides, but histopathological evaluation usually resolves the dilemma.

Background

Pfeifer-Weber-Christian disease (PWCD), also known as idiopathic relapsing febrile lobular non-suppurative panniculitis, is characterized by recurrent subcutaneous inflammatory painful nodules, varying from 1 to 12 cm in diameter, occurring on arms and legs and less frequently on chest back, abdomen, feet and face. Fever and malaise due to systemic inflammation were frequently associated. Less often it was accompanied by generalized aching pains, loss of weight, nausea, headaches and joint pains [1].Viscelar parenchymatous organs (lungs, heart, intestines, spleen, kidney, adrenal glands, and even orbits) as well as viscelar adipose tissue (messenteric, omental, pericardial and pleural tissue) can be involved in PWCD cases [1, 2]. Etiopathogenesis of the disease is not fully known, participation of autoimmune mechanisms is anticipated. The diagnosis of PWCD is a diagnosis of exclusion when no other cause for the lobular panniculitis can be identified [3, 4].

Angiolipomas are rare, benign subcutaneous tumors, composed of adipose tissue and blood vessels and often containing fibrin thrombi, that account for approximately 10% of tumors of fat. These lesions may be present as either singular or, more frequently, multiple subcutaneous masses in the limbs and trunk, but have been documented in other areas including spinal region, paratesticular region, breast, gastric, orbit, lungs, finger, foot, oral cavity, kidney, etc [5]. The majority of angiolipomas occur sporadically; however, there is a minority of cases that have been associated with familial inheritance patterns [6] and

the use of certain medications such as Indinavir (protease inhibitor used in the treatment of human immunodeficiency virus (HIV)) [7] or long-term corticosteroid use [8].

In this report, we described an unusual case of PWCD associated with benign multiple subcutaneous noninfiltrative angiolipomas (BMSNA) which gradually increased in size during corticosteroid therapy. To the best of our knowledge, there are no previous reports of this association (from 1944 to 2019).

Case Presentation

A 46-year-old white woman was admitted to the Institute of Rheumatology (June 2017), because of a painful subcutaneous nodule on her face (right masseteric cheek) with erythema in overlying skin associated with fever, oral aphthous ulcers, arthralgia/arthritis, myalgia, dry eyes and mouth, Raynaud's phenomenon and generalized weakness. This condition started in 2002. From 2002 to 2017, she had biyearly flares of panniculitis. In 2017 flares recurred every month. Initially, the nodules spontaneously withdrew. Later, she received anti-inflammatory, local anti-edematous, and antibiotic therapy, as well as large or small doses of corticosteroids with no improvement. Also, she had multiple palpable subcutaneous masses on the surface on her body (lower trunk, arms and upper legs) since 2013. These tumours were symmetrical, painless, with a consistence suggestive of lipomas, but unlike the lipomas, they were not encapsulated.

Personal history revealed depression since 2008, high cholesterol and triglycerides since 2010, left adnexectomy and right salpingectomy in 2012 due to left tubo-ovarian abscess and bilateral pyosalpinx, radical hysterectomy in 2015 due to chronic salpingitis and oophoritis, and allergy to penicillin. There was no known tubercular contact or a family history of a similar disorder.

Clinical examinations revealed circumscribed mass in the right masseteric space, ovoid in shape, firm, tender with mild erythema in overlying skin, no fluctuation, with a dimple in the center, as well as bilateral, symmetric, soft, well-circumscribed round subcutaneous masses involving lower trunk, forearms and upper legs. These masses varied in size from 1 cm x 1 cm to 6 cm x 4 cm (Fig. 1a-b). Her body height was 172 cm, body weight was 69.3 kg and body mas index was 23.4 kg/m^2. The percentage of fat was 34.9%, and fat mass was 24.2 kg (normal range 23–34%, vs 13.5–23.2 kg, respectively, Tanita analyzer). Complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies (ANA), anti-neutrophilic cytoplasmic autoantibody, anticyclic citrullinated peptide, rheumatoid factor, anti Ro/SSA, anti La/SSB antibody, anticardiolipin antibody, anti-beta 2 glycoprotein-I antibody, cryoglobulins, immunoglobulin assay, protein electrophoresis, immunoelectrophoresis, IgG4, C1 inhibitor and $C1_{q,}$ circulating immune complexes, complement C3 and C4 levels, serum amylase, alpha 1-antitrypsin, angiotensin-converting enzyme, were all negative/normal. The renal functions and the electrolytes were also all normal. The urine was free of any sediments or protein. HLA B51 was negative. Hepatitis B and hepatitis C virus, HIV, Brucella abortus bovis test and dirofilaria repens test were negative. The chest radiograph and the abdominal ultrasonography were normal.

Salivary ^{99m} Tc-pertechnetate scintigraphy showed decreased accumulation an excretory function in both parotid and submandibular glands. A salivary gland biopsy showed nonspecific sialoadenitis gradus 0. Lissamine green and Schirmer's test were negative. Capillaroscopy was normal. Dual-energy X-ray absorptiometry scanning showed osteopenia (T-score of total hip was − 1.0, and spine − 1.4). Ultrasound of the forearm showed subcutaneous masses of nonencapsulated adipose tissue with internal vascularity (Fig. 2a-b).

A skin biopsy (right masseteric cheek) showed intact and normal epidermis. The subcutaneous fat showed focal lobular lymphocytic infiltration around small blood vessels along with slightly widened interlobular septum with rare epithelioid granulomas (Fig. 3a). Granulomas were composed solely of epithelioid histiocytes, without necrosis or giant cells and rare granulomas were surrounded with lymphocytes (Fig. 3b). Focally, small areas of fat cell necrosis and foamy histiocytes (lipophagic panniculitis) were noted, unrelated to granulomas (Fig. 3c).

The endocrinology investigation revealed the following pathologic parameters: cholesterol 9.46, LDL-cholesterol 5.12 and triglycerides 2.23 mmol/l (normal range < 5.2 vs < 3.4 vs < 1.7 mmol/l, respectively), and autonomic neuropathy. She was absence of insulin resistance. Treatment for dyslipidemia was Rosuvastatin 20 mg/day, Esetimibe 10 mg/day, but with unsatisfactory values of total cholesterol and LDL-ch. All other endocrine parameters such as the thyroid hormones, catecholamines in 24 h urine, cortisol, adrenocorticotropic hormone, dehydroepiandrosterone sulfate, prolactin, human growth hormone, parathyroid hormone, neuron-specific enolase and chromogranin A were normal. The luteinizing hormone and follicle-stimulating hormone showed iatrogenic menopauses.

We established the diagnosis of PWCD and BMSNA, after other types of panniculitis and multiple lipomas were excluded (Table 1, Table 2). Treatment options was prednisone 20 mg/day. Angiolipomas were treated conservatively, because patient had no other complaints related to the excess fat tissue.

Table 1
Classification of panniculitis and conditions associated with panniculitis

Type of panniculitis
I. **Lobular panniculitis**
1. Pfeifer-Weber-Christian disease (Idiopathic relapsing febrile lobular non-suppurative panniculitis)
2. Panniculitis in systemic connective tissue diseases: (Systemic lupus erythematosus, Rheumatoid arthritis, Vasculitis, Myositis, Systemic sclerosis, Eosinophilic fasciitis, Eosinophilia-myalgia syndrome)
3. Complement deficiency
4. Lipodystrophic panniculitis
5. Enzymatic panniculitis: (pancreatitis, pancreatic carcinoma, alpha-1-antitrypsin deficiency)
6. Factitial panniculitis
7. Cytophagic histiocytic panniculitis
8. Post-steroid panniculitis (withdrawal of glucocorticoids)
9. Hodgkin’s lymphoma and leukemia
10. Rothmann-Makai syndrome (Lipogranulomatosis subcutaneous)
II. **Septal panniculitis**
1. Erythema nodosum
2. Subacute nodular migratory panniculitis (Vilanova disease)
III. **Mixed panniculitis**
1. Lupus profundus panniculitis
2. Erythema nodosum-like lesions in Behcet's syndrome
IV. **Panniculitis with vasculitis**
1. Vasculitis of small blood vessels
2. Medium-size vessel vasculitis (small arteries or arterioles)
3. Polyarteritis nodosa
4. Erythema induratum (nodular vasculitis)

Table 2
Rare syndromes associated with lipomas

Syndrome	Components
Familial angiolipomatosis	Family history of similar lesions, autosomal-recessive or autosomal-dominant fashion
Benign symmetric lipomatosis (Madelung's disease, Launois-Bensaude's syndrome)	Diffuse or circumscribed symmetrical accumulation of adipose tissue, primarily around the neck, back, shoulders and upper trunk
Neurofibromatosis type I	Café au lait macules, cutaneous/subcutaneous neurofibromas, axillary or groin freckling, optic pathway glioma, nodules, bony dysplasia
Cellular angiolipoma	Histologic are composed almost entirerly of small vessels (> 95% of the lesion)
Spindle cell-lipoma	Subcutaneous nodule in the head and neck region, composed of mature adipocyte and bland spindle cells
Angiomyxolipomas	Contains mature adipose tissue, extensive myxoid stroma nad numerous blood vessels
Lipomatosis syndrome in patients infected with HIV	Lipomas, peripheral lipodystrophy, central adiposity, dyslipidemia, inulin resistence
Bannayan-Zonana syndrome	Multiple lipomas, hemangiomas, macrocephaly
Cowden disease	Lipomas, hemangiomas, goiter, various skin and mucosal lesions (including intraoral papillomas, acral keratoses, facial trichilemomas), colorectal hamartomatous polyps, gastric polyps with hyperplastic features
Fröhlich syndrome	Multiple lipomas, sexual infantilism, obesity
Proteus syndrome	Pelvic lipomatosis, fibroplasia of hands and feet, skeletal hypertrophy, bony exostoses, scoliosis, pigmented skin lesions

Due to poor control of main disease and rapid angiolipoma growth on forearms (approximately 10 × 10 mm to 25 × 17 mm) corticosteroids were discontinued after two month of use. The patient underwent surgical excision. Tumor measured 25 × 15 × 10 mm in size. It was encapsulated yellow adipose tissue with a smooth surface at the intersection with red areas corresponding to blood vessels (Fig. 4a). Microscopically, tumour were composed of the lobules of mature adipose tissue with focally grouped, branching capillaries (Fig. 4b). Hyaline thrombi were found in capillaries (Fig. 4c).

After surgical excision patient was treated with cyclosporine A (CyA), 6 mg/kg/day for 12 months. As she was with no disease activity reported and no new tumour growth CyA dose was reduced to 2.5 mg/kg/day. Eight months after the dose reduction, patient was readmitted due to one-month history of abdominal discomfort, weight loss, nausea, and vomiting, accompanied by arthritis, fever, and oral

aphthous ulcers. Appendectomy was performed. Apendix was 45 mm long, 6 mm in diameter, turbid serose and wall thickening surrounded with many adhesions. Due to pronounced peritoneal adhesiones, the mesoappendix was difficult to see but seemed to be unchanged. The histopathological analysis revealed acute phlegmonous appendicitis. The dose of CyA was increased to 6 mg/kg/day. Patient is currently disease-free with no new growth of angiolipomas.

Disscusion And Conclusions

PWCD is one of many rare diseases that may be easily missed if there is not a high degree of suspicion. Owing to its rarity, our patient suffered from flares of disease that were not recognized and diagnosed for 15 years. At first, our medical team did not ascribe this patient's manifestations to PWCD. Subsequently, an Internet search was made, which helped to diagnose. We searched PubMed, Web of Science, and Scopus for cases of PWCD published from 1944 to December 1st, 2019, as well as cases of angiolipomas published from 1989 to December 1st, 2019. The search terms were Pfeifer-Weber-Christian disease, Weber Christian diseases, idiopathic relapsing febrile lobular non-suppurative panniculitis, idiopathic lobular paniculitis, angiolipomas, multiple symmetric lipomatosis, benign symmetric lipomatosis. Some 617 cases (264 in English, 317 in another languages other than English, and 36 cases of children) and 5 case series with 63 PWCD patients have been reported in the world-wide literature. More than 160 cases in English with angiolipomas have been reported in the literature. Although the most common sites are the forearm, followed by the trunk and upper arm [9], published cases show rare localizations of angiolipomas (86 cases with spinal extradural angiolipomas, 30 cases with angiolipoma in gastrointestinal tract, in 11 cases angiolipomas were localized in breast, in 6 cases in mediastinum, 6 in kidney, 6 in brain, 6 in cranium, 4 cases in the lung and 4 in the foot, 3 cases in the orbita, 3 in the testicular or paratesticular region, 2 cases in the finger and 2 cases in the knee). All articles were screened and only English articles containing information regarding search terms were considered and evaluated. There are no previous reports of association between PWCD and BMSNA.

In our patient, the diagnosis of PWCD was made based on the clinical features (painful swellings on the face associated with fever, generalized weakness, arthralgia, arthritis, myalgia), and histopathological findings of the skin nodule (inflammation of adipose tissue with lymphocytes, fat necrosis and lipophagia), after other types of panniculitis, such as those associated with pancreatitis, alpha 1-antitrypsin deficiency, systemic lupus erythematosus, vasculitis, thrombophlebitis, sarcoidosis, as well as histiocytic cytophagic panniculitis and factitial panniculitis were excluded (Table 1).

Unlike other cases published in the literature, our patient had less frequent, as well as asymmetric localization of inflammatory painful nodules on the face. Besides typical histological findings observed in PWCD such as lobular paniculitis with lymphocytic infiltration around small blood vessels and focal necrosis of fat cells without septal involvement or vasculitis, our patient also had unusual histological findings such as lipophagia and granulomas. Lipophagia and granulomas led to confusion in the context of erythema nodosum, but focal necrosis of fat cells is not typical for it [3]. Erythema nodosum has been

classified as predominantly septal panniculitis, unlike findings in PWCD being classified as lobular panniculitis [10, 11].

The prognosis of PWCD depends on which organs are affected, as well as on the response to therapy. The clinical course in our patient was characterized by exacerbations and remissions of the cutaneous lesions for 15 years before the disorder attacked the intestine. Although we have not proved it, on the basis of clinical findings and literature review we assume that our patient suffered from mesenteric panniculitis as well. Mesenteric panniculitis was first identified by Jura back in 1924 [12]. It is a fibroinflammatory condition of uncertain etiology. It is characterized by nonspecific inflammation, necrosis and fibrosis of the adipose tissue. It usually involves the mesentery of the small bowel, appendix, mesoappendix and, less frequently, the sigmoid or other intraabdominal fatty tissue. It can regress spontaneously, run a stationary course or progress to varying degrees of fibrosis [13]. Our patient had abdominal discomfort, weight loss, nausea and vomiting. Histological findings showed acute inflammation of appendix. In two large case series, a history of abdominal surgery (cholecystectomy or appendicectomy) was noted in about 40% of the patients with the mesenteric panniculitis [14, 15].

The rarity of PWCD makes it hard to assess the response of the disease to the therapeutic strategies. Accordingly, treatment options are empiric. They are derived on the basis of individual cases. Drugs used in the treatment of PWCD include corticosteroid therapy, fibrinolytic agens, hydroxychloroquine, azathioprine, thalidomide, cyclophosphamide, tetracycline, CyA, mycophenolate mofetil and anti-TNF treatment [4, 16–19]. CyA and corticosteroids have been proved most effective [4, 20–22]. In the present case, we also showed successful response to CyA. Cyclosporine A has potent immunosuppressive properties that result from selective inhibition of T-lymphocyte activation. This suggests that the T-lymphocyte may have an important role in the pathogenesis of PWCD.

In our patient corticosteroid therapy was discontinued after two months since there was a rapid increase in tumor mass on the forearms. Histopathologic evaluation of the masses removed was consistent with angiolipoma. The literature has shown few cases associating long-term corticosteroid use with the development of lipomas in the spinal epidural space [23–25] and mediastinum [26]. Only one case [8] described an association between long-term immunosuppression (azathioprine and prednisone) secondary to a bilateral kidney transplant and the development of subcutaneous angiolipomas in upper and lower extremities. Beside angiolipomas, there was a report of another epidural lipomatous tumour, a hibernoma in a 6-year-old child with juvenile rheumatoid arthritis treated with prednisone for four years [27]. We believe this case represent spinal lipomatosis with remnants of brown fat cell rather than a true tumour. Exogenous-steroids-induced angiolipomas were also described in a young male after misuse of anabolic steroids [28]. A variable length of period from initiation of steroid use till appearance of lipomatosis or angiolipomas and presence of androgen receptors expression in angiolipomas suggest anabolic effects of steroids, rather than immunosuppression, as a mechanism of fat cell proliferation. Angiolipomas are widely associated with diabetes mellitus [29] or are known as a complication of antiretroviral therapy [7]. In our case, the patient was neither a diabetic nor immunocompromised with HIV.

Histopathological findings in angiolipoma, with lobules of mature adipocytes and proliferation of capillaries with focal hyaline thrombi, enable easy diagnosis. Diagnostic difficulties can occur in cases with a prominent proliferation of capillaries and small amount of fat tissue [30]. In our case, histopathological appearance was typical, and diagnosis was easily made.

Clinically, angiolipomas are painful and relatively small tumors (< 2 cm) with a predilection for the upper extremities, and most commonly occur at an earlier age (second and third decades of life), usually in male patients [31, 32]. In our case the patient was female and was older than most reported cases in the literature. Howard et al. reported 288 angiolipomas in 248 patients, with male predominance and men age starting from 17 years [33]. Also, our patient's tumor was asymptomatic in accordance with a report mentioning that angiolipomas may sametimes be asymptomatic [34, 35].

In conclusion, the presented case illustrated a typical problem of every patient suffering from rare disease. It is important to distinguish PWCD and BMSA from other rare syndromes associated with panniculitis and lipomas. This case specifically highlights the histopathological aspects of PWCD and angiolipoma as a vital clue to the diagnosis, and supports the hypothesis that PWCD is a T cell mediated autoinflammatory condition, and may represent an association between long-term corticosteroid use and the growth of angiolipomas. We hope that our experience will increase greater awareness of these rare disorders.

List Of Abbreviations

PWCD: Pfeifer-Weber-Christian disease; BMSNA: Benign multiple subcutaneous noninfiltrative angiolipomas; HIV: Human immunodeficiency virus; ANA: Antinuclear antibodies; CyA: Cyclosporine A.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal. Since no human experimentation was performed, no approval by an ethics board was required.

Consent for publication

The written informed consent for publication was obtained from the patient.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

SPD and GR initially saw the patient and formulated the presented idea. SPD, TM, MB, NVS, IJ, and DD performed literature review, investigated details pertaining to the patient's presentation and formulated the case description, discussion, case reviews and created associated tables. GR, NVS, TM, MB and SPD verifed the accuracy of literature review and case descriptions, and assisted in final editing. All authors discussed the manuscript and agreed on changes made prior to submission. All authors read and approved the final manuscript.

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Figures

Figure 1

a) Induration of the skin in the right masseteric space b) Multiple well-circumscribed, round subcutaneous tumours in the forearms of patient

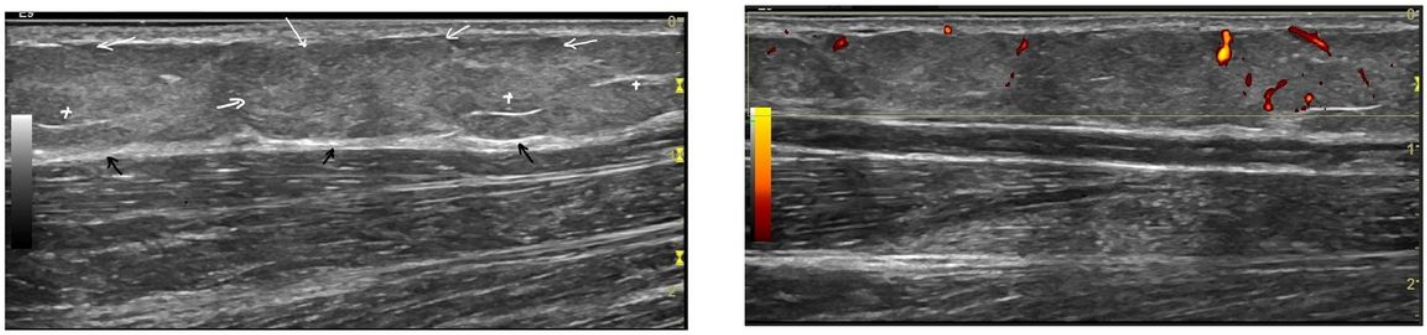
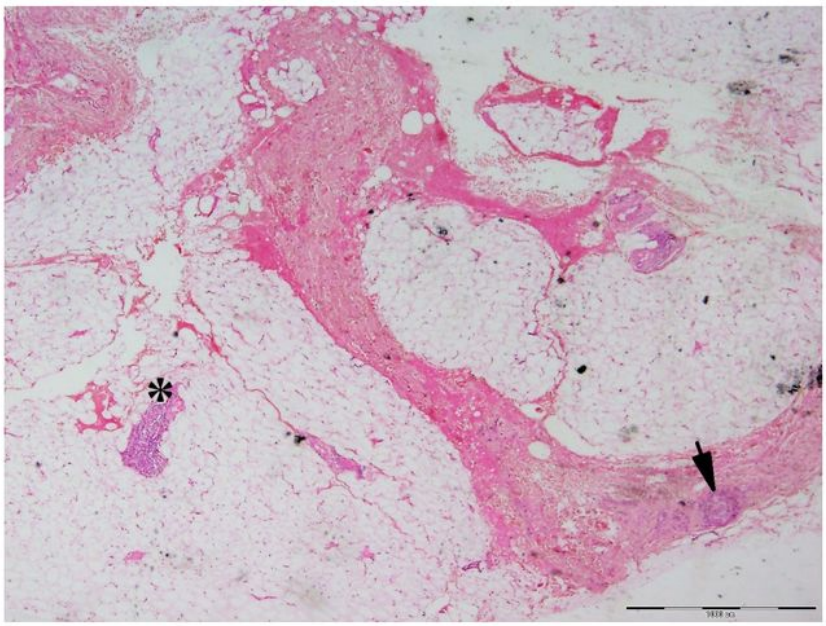
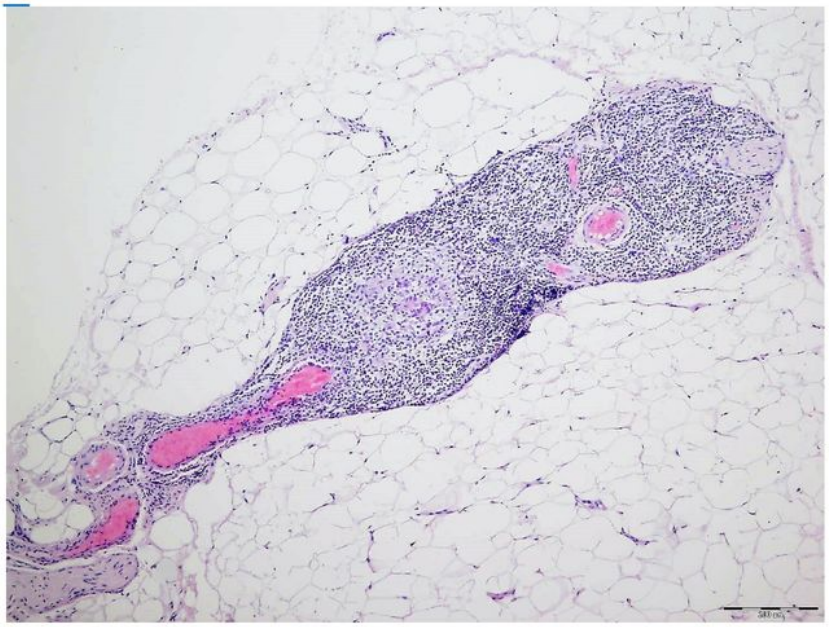


Figure 2

Sonograms angiolipomas in patients forearms a) On the grayscale sonogram, there are 3 heterogeneous hyperechoic ovoid masses in the subcutaneous layer. Their lateral and superficial tumor capsules (white arrows) are not visualized, whereas the deep tumor capsules (black arrows) are well visualized. Internal echogenic strands (white cross) are seen within them b) The power Doppler sonogram showed presence of vascularity



3a

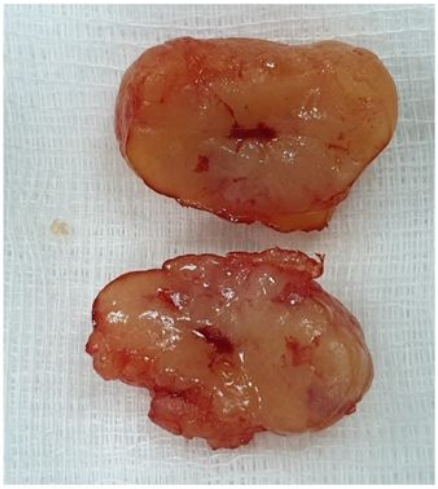


3b

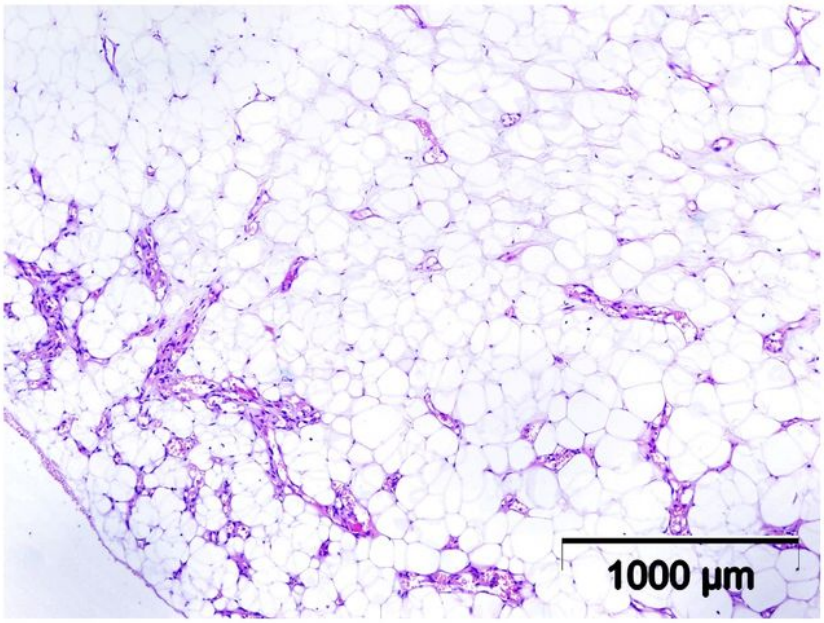
Figure 3

The photomicrograph a) Focal lobular lymphocytic infiltration around small blood vessels (asterisk) along with slightly widened interlobular septum with rare epithelioid granulomas (arrow). (Haematoxylin and Eosin staining, magnification x40) b) Granulomas were composed of epithelioid histiocytes and lymphocytes, without necrosis or giant cells (Haematoxylin and Eosin staining, magnification x100) c)

Rare small areas of fat cell necrosis and foamy histiocytes (lipophagic necrosis) were noted, unrelated to areas with granulomas (magnification x400)



4a



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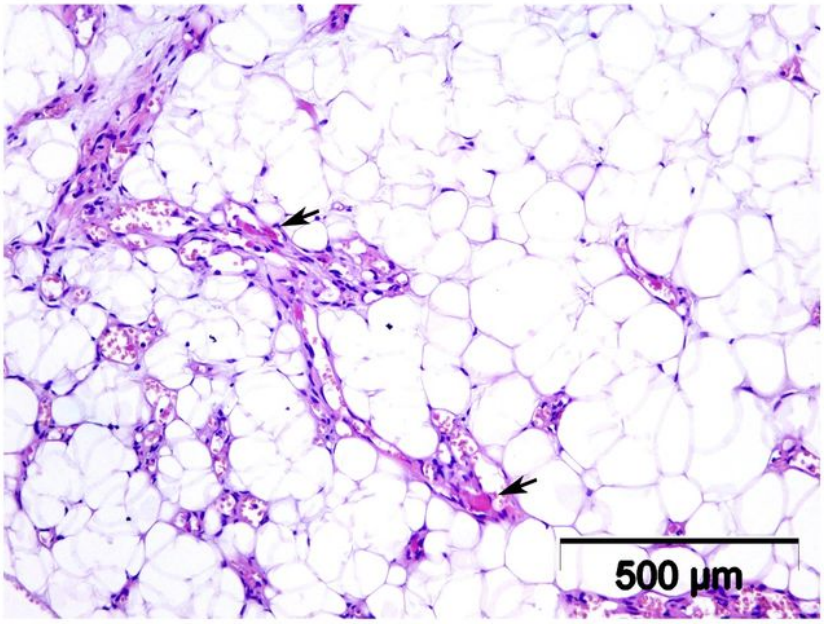

4c

Figure 4

Angiolipomas a) Macroscopic encapsulated yellow adipose tissue with red areas corresponding to blood vessels b) On histopathology, in lobules of mature adipose tissue focally grouped branching capillaries were seen (Haematoxylin and Eosin staining, magnification x100) c) Some of capillaries contained

hyaline thrombi (arrows) enabling diagnosis of angiolipomas (Haematoxylin and Eosin staining, magnification x200)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- patientconsentform.jpg