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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Corticosteroid treatment and growth of angiolipomas in patient with two rare diseases: Pfeifer–Weber–Christian disease and benign multiple subcutaneous angiolipomas

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SUMMARY
Introduction Pfeifer–Weber–Christian disease (PWCD) is a rare inflammatory disorder of the subcutaneous fatty tissue. Angiolipoma, is a benign adipocytic soft tissue tumor composed of mature adipose tissue and small vascular proliferations. Treatment with corticosteroids could lead to proliferation of fat tissue but the stimulation of angiolipoma growth during corticosteroid therapy is extremely rare.
Case outline We describe a case of a 46-year-old female patient with histopathological confirmation two rare diseases: PWCD and benign multiple subcutaneous non-infiltrative angiolipomas. Angiolipomas were treated conservatively. Treatment for PWCD was prednisone 20 mg/day. Due to poor control of PWCD and rapid angiolipomas growth on forearms, corticosteroids were discontinued after two months of use. Administration of oral cyclosporine A led to a rapid remission of the PWCD, and with no new growth of angiolipomas.
Conclusion The successful therapy with the Cyclosporine A supports the hypothesis that PWCD is a T cell mediated autoinflammatory condition. Rapid growth of angiolipoma during corticosteroid therapy is an extremely rare condition.
Keywords: prednisone; angiolipoma; side effect; panniculitis

INTRODUCTION

Pfeifer–Weber–Christian disease (PWCD), is a rare idiopathic disease characterized by lobular panniculitis of adipose tissue with systemic symptoms and multiple organ involvement and is usually treated with corticosteroids [1]. 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 [2]. For now, the induction of growth of angiolipoma during corticosteroid treatment, was reported only in one case [3].

We described an unusual case of PWCD associated with benign multiple subcutaneous non-infiltrative angiolipomas, which gradually increased in size during corticosteroid therapy. To the best of our knowledge, there are no previous reports of this association (1944–2020).

CASE REPORT

A 46-year-old Caucasian female presented with relapsing and remitting biyearly flares of panniculitis (always masseteric space, where appear subcutaneous painful nodules with erythema in overlying skin) (Figure 1a), associated with fever, oral aphthous ulcers, arthralgia/arthritis, myalgia, and generalized weakness, for 15 years (2002–2017). Initially, the nodules spontaneously withdrew. Later, she received anti-inflammatory, local anti-edematous, and antibiotic therapy, with no improvement. In 2017, the disease recurred every month. A skin biopsy (right masseteric cheek) showed predominantly lobular panniculitis (Figure 1b–d). She also had multiple soft, well-circumscribed, round subcutaneous tumors present on lower trunk, forearms, and upper legs, distributed in a symmetric pattern, and ranged from 1 × 1 cm to 1.5 × 2 cm in size (Figure 2a). This condition started in 2013.

Her personal history revealed Raynaud's phenomenon, and dry eyes and mouth since 2002, high cholesterol and triglycerides since 2010, radical hysterectomy for chronic salpingitis and oophoritis 2015, and allergy to penicillin. There was no known tubercular contact or a family history of a similar disorder.

Her body height was 172 cm, body weight was 69.3 kg and body mass index were 23.4 kg/m^2. The percentage of fat was 34.9%, and fat mass

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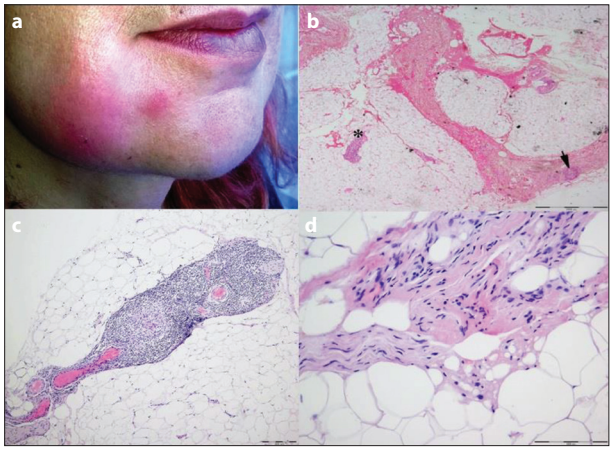

Figure 1. a – Induration of the skin in the right masseteric space; b – focal lobular lymphocytic infiltration around small blood vessels (asterisk) along with slightly widened interlobular septum with rare epithelioid granulomas (arrow), (hematoxylin and eosin staining, magnification × 40); c – granulomas were composed of epithelioid histiocytes and lymphocytes, without necrosis or giant cells (magnification × 100); d – rare small areas of fat cell necrosis and foamy histiocytes (lipophagic necrosis) were noted, unrelated to areas with granulomas (magnification × 400)

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, 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, IgG 4, 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 B27 and HLA B51 was negative. Hepatitis B and hepatitis C virus, human immunodeficiency virus, IGRA test for tuberculosis, *Brucella abortus bovis* test and dirofilaria repens test were negative. The chest radiograph and the abdominal ultrasonography were normal. Ultrasound of the major salivary gland was normal. Salivary ^{99m}Tc-pertechnetate scintigraphy showed decreased accumulation an excretory function in both parotid and submandibular glands. A salivary gland biopsy showed rare dispersed lymphocytes and plasma cells without acinar atrophy, a finding consistent with nonspecific sialadenitis (grade 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). 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. All other endocrine parameters such as the thyroid hormones, catecholamines in 24 hours 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. Ultrasound of the forearm showed subcutaneous masses of adipose tissue with internal vascularity suggestive of angiolipoma (Figure 2b–c).

We established the diagnosis of PWCD and benign multiple subcutaneous non-infiltrative angiolipomas, after other types of panniculitis and multiple lipomas were excluded (Table 1 and Table 2). Angiolipomas were treated conservatively, because patient had no other complaints related to the excess fat tissue. Treatment for dyslipidemia was rosuvastatin 20 mg/day, and Ezetimibe 10 mg/day, but with unsatisfactory values of total cholesterol and LDL cholesterol. Treatment for PWCD was prednisone 20 mg/day.

Due to poor control of PWCD and rapid angiolipoma growth on forearms (approximately 10 × 10 mm to 25 × 17 mm) corticosteroids were discontinued after two months of use. The patient underwent complete surgical excision of two tumors on forearms measured 25 × 15 × 10 mm and 22 × 13 × 9 mm, which were encapsulated and yellow with the appearance of adipose tissue with red areas corresponding to blood vessels (Figure 3a). Tumors were composed of the lobules of mature adipose tissue with focally grouped, branching capillaries and focal hyaline thrombi in capillaries, and were diagnosed as angiolipoma (Figure 3b–c).

Patient was treated with cyclosporine A, 6 mg/kg/day for 12 months. As she was with no disease activity reported and no new tumor growth cyclosporine A 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.

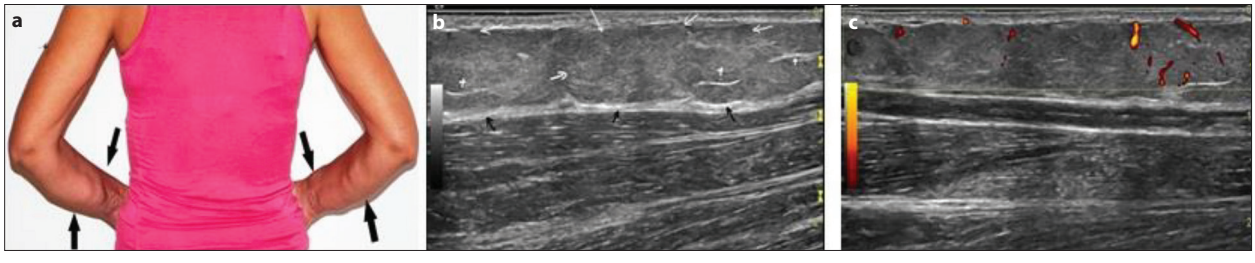

Figure 2. a – Multiple well-circumscribed, round subcutaneous tumors in the forearms of patient (black arrows); b – the grayscale sonogram of forearms tumors showed three heterogeneous hyperechoic ovoid masses in the subcutaneous layer, with internal echogenic strands (white cross), deep tumor capsules (black arrows), and no lateral and superficial capsules (white arrows); c – the color Doppler sonogram showed presence of vascularity

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)

The dose of cyclosporine A was increased to 6 mg/kg/day. Appendectomy was performed and histopathological analysis revealed acute phlegmonous appendicitis. Due to pronounced peritoneal adhesions, the mesoappendix was difficult to see but seemed to be unchanged. The patient is currently disease-free with no new growth of angiolipoma.

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

DISSCUSION

Clinically, angiolipoma 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 [2, 4]. In our case, the patient was female and was older than most reported cases. In literature, appearance of numerous angiolipoma after corticosteroid therapy was reported only once, in a male patient after 15-year-long therapy with prednisone and azathioprine in the treatment of bilateral kidney transplantation [3]. In our case, tumors have already been present before the initiation of therapy. Their growth was induced after only two months of prednisone treatment.

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 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 entirely 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
Angiomyxolipoma	Contains mature adipose tissue, extensive myxoid stroma and numerous blood vessels
Lipomatosis syndrome in patients infected with human immunodeficiency virus	Lipomas, peripheral lipodystrophy, central adiposity, dyslipidemia, insulin resistance
Bannayan–Zonana syndrome	Multiple lipomas, hemangiomas, macrocephaly
Cowden disease	Lipomas, hemangiomas, goiter, various skin and mucosal lesions (including intraoral papillomas, acral keratoses, facial trichilemmomas), 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

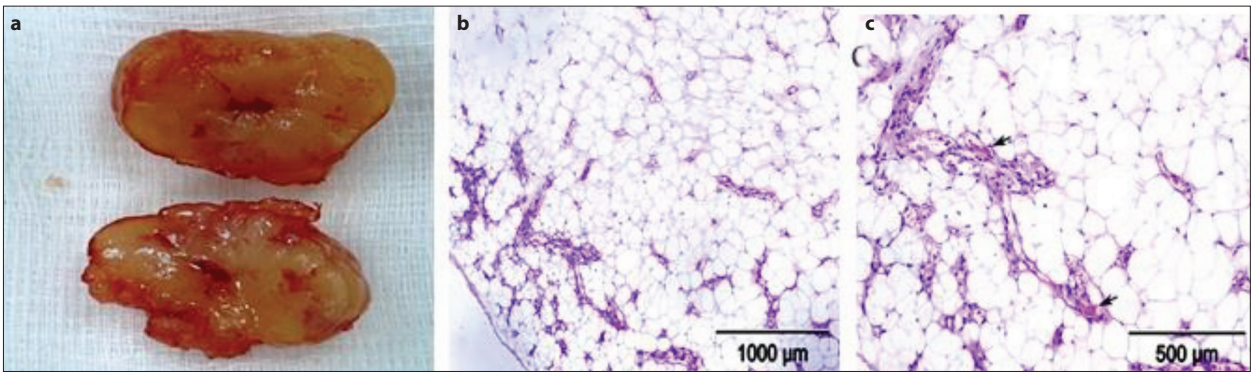

Figure 3. a – Macroscopic encapsulated yellow adipose tissue with red areas corresponding to blood vessels; b – on histopathology, in lobules of mature adipose tissue focally grouped branching capillaries were seen (Hematoxylin and Eosin staining, magnification × 100); c – some of capillaries contained hyaline thrombi (arrows) enabling diagnosis of angiolipomas (Hematoxylin and Eosin staining, magnification × 200)

Exogenous-steroids-induced angiolipoma were also described in a young male after misuse of anabolic steroids [5]. A variable length of period from initiation of steroid use till appearance of lipomatosis or angiolipoma and presence of androgen receptors expression in angiolipoma suggest anabolic effects of steroids, rather than immunosuppression, as a mechanism of fat cell proliferation [2, 3, 6]. Beside angiolipoma, there was a report of another epidural lipomatous tumor, a hibernoma in a six-year-old child with juvenile rheumatoid arthritis treated with prednisone for four years [7]. We believe this case represent spinal lipomatosis with remnants of brown fat cell rather than a true tumor.

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 [4]. In our case, histopathological appearance was typical, and diagnosis was easily made.

However, the panniculitides are heterogenous inflammatory diseases of subcutaneous fat tissue that could bring diagnostic challenge and require thorough clinicopathological exploration [1, 8]. This is especially true in case of lobular panniculitides where a detailed clinical and histopathological evaluation led to reassessment of an entity previously known as PWCD. Because morphological findings in such biopsies pointed out to other specific diseases, it was suggested this term should be abandoned in dermatology [9]. However, in our case other types of panniculitides were excluded and diagnosis of PWCD was made.

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 agents, hydroxychloroquine, azathioprine, thalidomide, cyclophosphamide, tetracycline, cyclosporine A, mycophenolate mofetil, anti-TNF treatment and intravenous immune globulin therapy [1, 10, 11, 12]. Cyclosporine A and corticosteroids have been proved most effective [11, 13]. In the present case, we also showed successful response to cyclosporine A. 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.

To conclude, presented case illustrated a typical problem of every patient suffering from rare disease – a too long period of time from the onset of symptoms to diagnosis and treatment. PWCD and benign multiple subcutaneous non-infiltrative angiolipomas represents diseases with a broad spectrum of symptoms and thus also a difficult differential diagnosis that require patience of the physician. 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 corticosteroid use and the growth of angiolipomas. We hope that our experiences will also can contribute to greater awareness of these rare disorders.

This article has been posted as a preprint on Research Square.

Conflict of interest: None declared.

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Лечење кортикостероидима и пораст ангиолипома код болеснице са две ретке болести: Фајфер–Вебер–Кристијанова болест и доброћудни вишеструки неинфилтрирајући ангиолипоми

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САЖЕТАК

Увод Фајфер–Вебер–Кристијанова болест (ФВКБ) редак је инфламаторни поремећај поткожног масног ткива. Ангиолипом је бенигни адипоцитни тумор меког ткива који се састоји од зрелог масног ткива и малих васкуларних пролиферација. Лечење кортикостероидима може да доведе до умножавања масног ткива, али је стимулација раста ангиолипома током терапије кортикостероидима изузетно ретка.

Приказ болесника Приказујемо болесницу стару 46 година која има хистолошку потврду две ретке болести: ФВКБ и доброћудне вишеструке неинфилтрирајуће ангиолипоме. Ангиолипоми су лечени конзервативно. ФВКБ је лечена преднизоном 20 *mg*/дан. Због лоше контроле ФВКБ и брзог раста ангиолипома на подлактици, кортикостероиди су прекинути после два месеца употребе. Примена оралног циклоспорина А довела је до брзе ремисије ФВКБ и није било новог пораста ангиолипома.

Закључак Успешна терапија циклоспорином А подржава хипотезу да је ФВКБ аутоинфламаторно стање посредовано Т-ћелијама. Убрзан раст ангиолипома током кортикостероидне терапије изузетно је ретко стање.

Кључне речи: преднизон; ангиолипом; нежељени ефекат; паникулитис