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Actinic Superficial Folliculitis after Sun Exposure in a 29-Year-Old Woman

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Abstract

The authors report the clinical case of a 29-year-old Caucasian woman who presented with clinicopathological findings and a previous outbreak all suggestive of actinic superficial folliculitis, a rarely reported and probably misdiagnosed phototoxic sun-induced dermatosis first described by Nieboer in 1985. Despite the exuberance of this cutaneous eruption, it is usually auto-limited, reinforcing the importance of its knowledge, for eviction of unnecessary diagnostic tests and therapies. Mechanisms of pathogenesis postulated include ultraviolet A radiation and local heat. This photodermatosis presents as monomorphic, superficial, pustular, and non-pruritic folliculitis affecting the upper body but not the face, usually arising on neck, back, shoulders and upper trunk. The follicular pustules emerge 24 - 72 h after intense exposure to heat and/or sunlight and fade spontaneously in 5 - 10 days, without scarring. This patient showed a 48-hour latency period; the number of pustules and area of the body affected were proportional to the duration of the sunlight exposure; the eruption lasted approximately 10 days. Actinic superficial folliculitis has a specific histology with follicular subcorneal sterile pustules and a mixed inflammatory infiltrate around hair follicles, probably secondary to keratinocytes and Langerhans cells involvement in the immunomodulatory actions of ultraviolet radiation. Recurrence under identical conditions may occur, after a latency period of at least 4 weeks, but usually about 1 year. Actinic superficial folliculitis and related follicular conditions are probably underdiagnosed and subsequently there is insufficient scientific information available to clinicians. Being familiar with these entities is of the utmost importance, since it can be crucial for their management.

Keywords

Actinic Superficial Folliculitis, Subcorneal Sterile Pustules, Sun Exposure, Photodermatosis

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1. Introduction

Pustules are circumscribed collections of white blood cells and serous fluid. Many skin lesions will present with papules or vesicles (clear fluid); those presenting with pustules occur less frequently. It is important to recognize the morphological pattern of pustules because it may imply a different spectrum of differential diagnosis as well as treatment. While the differential diagnosis of pustules is broad, several defining features can aid in narrowing down the possibilities in an efficient manner: the patient’s age and general health, the distribution and the duration of the lesions. Many follicular conditions associated with exposure to intense sunlight or heat or with immune alterations have been described, namely actinic superficial folliculitis (ASF) [1]-[4], actinic folliculitis (AF) [5]-[7], acne aestivalis (AA) [8] [9], disseminate and recurrent infundibulofolliculitis (RIF) [10]-[12], steroid acne (SA) [13] [14] and cytotoxic folliculitis in acute graft-versus-host disease (CFGvHD) [15] [16]. These conditions share some clinical and histological similarities, as discussed below [3].

ASF is a rare phototoxic sun-induced dermatosis first described by Nieboer in 1985. Mechanisms of pathogenesis postulated include ultraviolet A (UVA) radiation and local heat [1] [2]. UVA radiation may predispose to inflammatory reactions in the hair follicle infundibulum, by an immune or irritative mechanism. This photodermatosis presents as monomorphic, superficial, pustular, and non-pruritic folliculitis affecting the upper body but not the face, usually arising on neck, back, shoulders and upper trunk. The follicular pustules emerge 24 - 72 hours after intense exposure to heat and/or sunlight and fade spontaneously in 5 - 10 days, without scarring [2]-[4]. ASF has a specific histology with follicular subcorneal sterile pustules and a mixed inflammatory infiltrate around hair follicles, probably secondary to keratinocytes and Langerhans cells involvement in the immunomodulatory actions of UV radiation. Recurrence under identical conditions may occur, after a latency period of at least 4 weeks, but usually about 1 year [3] [4].

The authors report the clinical case of a 29-year-old Caucasian woman who presented with clinicopathological findings and a previous outbreak all suggestive of ASF, a rarely reported and probably misdiagnosed acute photodermatosis. Despite the exuberance of this cutaneous eruption, it is usually a self-limited disease, reinforcing the importance of its knowledge, for eviction of unnecessary diagnostic tests and therapies [2]-[4].

2. Case Presentation

A 29-year-old Caucasian woman presented to the Emergency Department with an extensive cutaneous follicular pustulosis with surrounding erythema distributed over her neck, shoulders, upper trunk (Figure 1(a) and Figure 1(b)) and back (Figure 2). The face, arms and lower body were spared. Areas of the chest not exposed to the sun remained also free of lesions. The pustular lesions were non-pruritic, painless and aroused within 2 days of that year’s first sun exposure, even with the use of sunscreen. The number of pustules and area of the body affected were proportional to the duration of the sunlight exposure.

There were no other symptoms or significant epidemiological context. No medications or cosmetics had been used.

The patient had reported the same symptoms one year before, with less extensive follicular pustules emerging three days after her first sunbath in Summer. The pustules were also localized on her back, chest and shoulders, sparing the face and the areas of skin covered by the bra. Her general condition was then unaffected and the cutaneous eruption resolved spontaneously within 7 days. Her medical history was negative for common acne and other diseases and she had no relevant family history.

On the admission she was apyretic and hemodynamically stable and, besides the cutaneous eruption, physical examination was otherwise unremarkable.

Laboratory evaluation demonstrated elevated inflammatory markers (leukocyte count 15,130/µL with 85% neutrophils, C-reactive protein 110 mg/L). Hemoglobin, platelet count, ionogram, liver, renal and thyroid function tests, serum immunoglobulins IgA, IgM and IgG, serum protein electrophoresis and immunological study (complement, rheumatoid factor, antinuclear, anti-double-stranded DNA, antineutrophilic cytoplasmic, anti-Sjögren’s syndrome A/B and anti-thyroid antibodies) were normal. Arterial blood gasometry and urinalysis were also normal. Human Immunodeficiency Virus 1 and 2, Herpes simplex virus 1 and 2 (HSV 1 and 2), Varicella-Zoster virus (VZV) and Hepatitis C virus serologies were all negative (IgM and IgG). She was immune to Hepatitis B virus. VDRL and Antistreptolysin-O titer were negative. Chest X-ray was normal.

A skin biopsy was performed on the admission after dermatology internal consultation and subsequently histology revealed subcorneal sterile pustules with mixed inflammatory infiltrate with lymphocytes around hair
follicles infundibulum and sebaceous glands. Bacterial cultures were negative, ruling out *Staphylococcus aureus* folliculitis. Fungi were not identified on periodic acid-Schiff staining and cultures. Polymerase Chain Reaction of HSV and VZV in biopsy were negative. Blood cultures were also negative.

Empirical therapy with topical Fusidic Acid and intravenous Flucloxacillin 1 gm q6h was started on admission, before definite results of skin biopsy bacterial cultures, assuming the possibility of an infectious folliculitis.
due to gram-positive organisms (including Beta-lactamase-producing *Staphylococci*). She remained persistently apyrelic and hemodynamically stable. Flucloxacillin was stopped on the fourth day of treatment because there was no significant clinical or analytical improvement, skin biopsy histology performed on admission revealed subcorneal sterile pustules and no bacteria or fungi could be cultivated from the pustules.

The eruption lasted approximately 10 days and resolved without further treatment, leaving no scar. Inflammatory markers progressively normalized. Provocative phototest was not performed, but the typical distribution of pustules and the saving of the areas covered by her strapless bra reinforced the pathogenic importance of actinic radiation.

Given the past medical history, clinical features of the cutaneous eruption and the biopsy result, the most likely diagnosis was actinic superficial folliculitis.

The patient was followed in Dermatology and Internal Medicine consultation after hospital discharge. She had no recurrence of the skin rash during one year of follow-up.

### 3. Discussion

The characteristics of this case allowed the authors to rule out superficial pustular folliculitis (whether of infectious origin, or due to other factors such as cosmetics or occlusion), AF, AA, RIF and SA.

Superficial pustular folliculitis (infectious) is not induced by UVA light; skin biopsy histology of this patient revealed subcorneal sterile pustules and no bacteria or fungi could be cultivated from the pustules [2]. There was no history of preceding cosmetic use.

AF, AA, RIF and SA are follicular conditions associated with exposure to intense sunlight or heat or with immune alterations, showing some clinical and histological similarities with ASF. This entities affect the hair follicle only, preferentially the upper follicular epithelium. The follicular lesions present as papules (AF, AA, RIF, SA), pustules (AF, ASF) or papulopustules (RIF) [3]. Time to onset and fade of follicular lesions are also different. In AF, the lesions may arise on face, shoulders, upper trunk and upper arms; the onset usually occurs 4 to 24 hours after UVA light exposure and fade in days to months [3] [6] [7]. AA may onset 15 to 30 days after intense exposure to sun and fade in 3 to 6 months [3] [8] [9]. RIF usually presents from Spring to Autumn with pruritic follicular papules, rarely papulopustules, on neck, trunk, upper arms, buttocks, and proximal thighs; it usually fades in one to several months [3] [10]-[12]. SA may arise 10 to 14 days after corticosteroid therapy on shoulders, upper trunk, upper arms and face and fade in one to several months [3] [13] [14]. Histologically, none of these entities involves comedo formation, at least in the initial phases; infundibular spongiosis and/or necrosis is the most frequent initial finding [3].

There are few case reports detailing ASF. ASF was first described in 1985 by Nieboer, reporting two patients with a recurrent, monomorphic, superficial pustular folliculitis arising on the shoulders, upper trunk and upper extremities, 24 - 36 hours after exposure to sunlight [1]. A short time later, Verbov described two similar patients with a recurrent eruption of morphomorphic follicular lesions presenting as pustules of the shoulders, arms and trunk, during warm periods [5]. Labandeira et al. (1997) described the case of a 31-year-old man with sterile follicular pustules on the shoulders, trunk and arms, recurring every year within 48 - 72 hours of the year’s first exposure to the sun, with clinicopathological findings closely corresponding to those of ASF as described by Nieboer [3]. Jaeger et al. (2002) reported on a 30-year-old man who presented with an extensive superficial follicular pustulosis on his back, shoulders and upper chest after exposure to intense heat and subsequent sweating on a sunny day; the pustules arose within 24 - 36 hours afterwards and resolved within 10 days without treatment and without scarring [4]. La Berge et al. (2012) reported the case of a 29-year-old man who presented with a 5-year history of an intermittent follicular rash on his back and chest, occurring only when he was exposed to the sun, with his shirt off, 24 to 36 hours after the first sun exposure of the year and resolving spontaneously after 5 to 7 days. This was the first case in which provocative photo testing was done [2].

This case report provides further evidence about this unusual disease.

### 4. Conclusion

ASF and the described related follicular conditions are probably under diagnosed and subsequently there is insufficient scientific information available to clinicians. Being familiar with these entities is of the utmost importance, since it can be crucial for their management. The evolution of this case was, as expected, a highly favourable one, with complete resolution of clinical manifestations.
**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**Consent**

Written informed consent was obtained from the patient for publication of this Case report. A copy of the written consent is available for review by the Editor of this journal.

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Eruptive Lentigines after Adalimumab Therapy

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Abstract

Adalimumab, a TNF-alpha antagonist, is the first fully humanized recombinant immunoglobulin G1 (IgG1) monoclonal antibody. It is presently widely used in the systemic treatment of rheumatoid arthritis, inflammatory bowel disease, moderate and severe psoriasis and hidradenitis suppurativa. However, its administration is associated with a two-fold risk of severe and possibly fatal infections and in some rare cases with congestive heart failure, lymphoma, lupus-like syndrome, cytopenias, hepatotoxicity and development of demyelinating neurological disorders. Furthermore, the occurrence of various types of melanocytic skin lesions has been reported during treatment with adalimumab. In the present paper we report the case of a female psoriatic patient who developed eruptive lentigines following treatment with this compound.

Keywords
Lentigines, Melanocytes, TNF-α, Adalimumab, Psoriasis

1. Introduction

Emerging biologic agents target specific key mediators in the immunopathogenesis of various immune and inflammatory diseases [1] and presently include three distinct classes of compounds: The inhibitors of interleukin-12 (IL-12)/interleukin-23 (IL-23), interleukin-17 (IL-17) and the inhibitors of tumor necrosis factor-alpha (TNF-alpha). The members of the latter class (etanercept, infliximab, adalimumab) are widely used in the systemic treatment of various autoimmune and inflammatory diseases, including moderate to severe plaque psoriasis. Recently, the occurrence of various types of melanocytic lesions has been reported during treatment with TNF-alpha inhibitors [2]-[4]. In the present paper we report the case of a psoriatic female patient who developed eruptive lentigines, subsequent to treatment with adalimumab.

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2. Case Report

In January 2010 the dermatologist of a 75-year-old woman with a 35-year history of chronic plaque psoriasis with arthropathy initiated a subcutaneous treatment with 40 mg adalimumab (Humira, Abbott Laboratories Ltd, Athens, Greece) every second week. Pre-treatment assessment for tuberculosis with tuberculin test was negative and chest radiograph was normal.

In February 2013, after three years of continuous treatment with adalimumab, she was admitted to the Department of Internal Medicine with a tuberculous peritonitis which was successfully treated with rifampicin, isoniazid and ethambutol (to be reported elsewhere).

Because of a relapse of her chronic plaque psoriasis due to the discontinuation of adalimumab, the patient (Fitzpatrick skin type IV) presented to the Department of Dermatology, University of Patras, Greece in September 2013. Apart from the psoriatic lesions, physical investigation revealed the presence of numerous and disseminated asymptomatic brown macular lesions (Figure 1), that developed in a short span of time 2 months after onset of adalimumab therapy, on both the apparently normal skin and the resolving psoriatic plaques. Her family history for lentigines and melanoma was negative.

She had previously been treated by her home town dermatologists with different topical (corticosteroids, dithranol, emollients) and systemic regimens (cyclosporine, acitretin, leflunomide). However, she had received no phototherapy or photochemotherapy. Her past medical history was remarkable for coronary heart disease, paroxysmal atrial fibrillation and cataract.

Routine laboratory tests including a complete blood count, blood chemistry, urinalysis, immunological and serological investigations (tests for syphilis, HSV 1 & 2, HIV 1 & 2, hepatitis A, B and C and CMV) were performed. Their results were either negative or within normal limits and chest X-ray and electrocardiogram were unremarkable. An informed consent was obtained from her to perform the biopsies, take photographs and report her case.

Histological examination of the brown macular lesions obtained from various sites showed distinct prolongation of rete ridges and increased numbers of uniformly dispersed melanocytes in the basal layer with variable hyperpigmentation (Figure 2). Occasionaly, a sparse lymphohistiocytic infiltrate and considerable numbers of melanophages could be seen in the papillary dermis. Thus, the diagnosis of eruptive lentigines was established. Biopsy specimens of adjacent clinically unaffected skin were essentially normal (Figure 3). The patient was instructed to topically apply anthralin ointment 2% once daily (short contact therapy) on her psoriatic plaques. However, she was lost to follow-up.

3. Discussion

TNF-alpha is a cytokine known to play a significant role in the surveillance of infectious and neoplastic disorders [3]. Adalimumab, a TNF-alpha antagonist, is the first fully humanized recombinant immunoglobulin G1
(IgG1) monoclonal antibody. It exerts its inhibitory effects on TNF-alpha by occupying the corresponding binding site and competitively inhibiting the binding of this cytokine to its receptor (TNFR) [3] [5].

Adalimumab is presently widely used in the systemic treatment of rheumatoid arthritis, inflammatory bowel disease, moderate and severe psoriasis and hidradenitis suppurativa. However, its administration is associated with a two-fold risk of severe and possibly fatal infections (deep fungal infections, bacterial infections including reactivation of tuberculosis, atypical mycobacterial infections, parasitic infections) [6]. Furthermore, serious but relatively rare side effects of this compound include congestive heart failure, lymphoma (particularly hepatosplenic T-cell lymphoma), lupus-like syndrome, cytopenias, hepatotoxicity and development of demyelinating neurological disorders [6].

Cutaneous side effects of adalimumab include reactions at the injection site, lupus erythematosus, urticaria, pustular dermatoses, leukocytoclastic vasculitis, non-specific rashes and flare of psoriasis [7]. In some rare cases, the use of this compound has been reportedly associated with the occurrence of various types of melanocytic skin lesions, such as melanoma, nevi, hyperpigmentation and lentigines, with the latter representing the simplest
form of them.

Rapid development of hyperpigmented skin lesions is reportedly associated with chemotherapeutic agents and bullous disorders [8]. Phototherapy and photochemotherapy, but also topical corticosteroids and vitamin D derivatives are known to induce the occurrence of lentigines in treated psoriatic patients [9]. Our patient has never received phototherapy, photochemotherapy or topical vitamin D derivatives. About two decades prior to her presentation to the Department of Dermatology she had been treated with topical steroids; it seems very unlikely, however, that the occurrence of eruptive lentigines may be attributed to the latter.

To the best of our knowledge, the patient presented here is the second case who developed eruptive lentigines subsequent to adalimumab therapy. In both, the case reported by Santos-Juanes et al. (2008) [10] and in our case, the development of these lesions started two months after the onset of treatment. This chronological association between adalimumab administration and the development of eruptive lentigines suggests that this drug may be implicated in the etiopathogenetic mechanisms of the latter. Since an intact immune system normally inhibits the proliferation of melanocytic lesions [11], it seems likely that the immunosuppression caused by adalimumab either leads to a dysregulation of melanocytic stem cell division [12] or facilitates the rapid and possibly uncontrolled proliferation of melanocytes in genetically predisposed patients [13] [14].

Furthermore, since the induction of cutaneous benign and malignant melanocytic proliferation seems to be a property shared by adalimumab and all other biologic agents, in patients who are treated with these compounds a close monitoring during treatment and a rigorous follow-up are highly recommended.

4. Conclusion

The results of the present paper taken together with those reported by other groups, clearly indicate that adalimumab and all other biologic agents, apart from their significant and serious side effects, are capable of inducing the cutaneous benign and malignant melanocytic proliferation. Thus, a close monitoring during treatment and a rigorous follow-up of patients treated with these compounds, are of essential importance.

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Continued Diagnostic Difficulties in Preoperatively Differentiating Lipiodized Oil and Residual Metallic Material: A Case Report

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Abstract

Retained foreign objects in the abdomen and pelvis are serious clinical problems yet the imaging required can present difficulties. Prolonged retention of lipiodized oil used for hysterosalpingography over years is very rare. However, lipiodized oil had previously been misdiagnosed as residual metallic material. We are reporting a case in which the latest computed tomography (CT) equipment seemed inadequate for obtaining a clear pre-operative diagnosis. Here, we describe the case of a 33-year-old Japanese female whose pelvis had contained retained lipiodized oil that had been suspected as residual metallic material. The preoperative diagnosis was very difficult and included three-dimensional computed tomography (3D-CT) of unclear results despite expectations of resolution. By laparoscopic surgery, we removed a cyst of approximately 2 cm containing a yellowish oily fluid. Postoperatively, we demonstrated that the fluid was lipiodized oil. A postoperative experiment to attempt distinguishing lipiodized oil from metal through gemstone spectral CT imaging did not offer clarity either. Distinguishing between retained lipiodized oil and metallic material in the abdominal cavity may still present unexpected difficulties even with the latest medical equipments.

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1. Introduction
Retained surgical materials in the abdomen and pelvis can present serious clinical problems; yet their imaging appearances have been reported as potentially confusing and difficult to interpret [1]. Risk factors for retention of surgical materials include emergency operation, unplanned change of procedure, and high patient body mass index. Although materials such as surgical sponges will become profoundly symptomatic in the early postoperative period, it is possible for lipiodized oil, which is often used for hysterosalpingography, to remain unnoticed for months or years without symptoms [1] [2]. There is a previous report of retained lipiodized oil, within the pelvis, mimicking a retained metallic foreign body that was removed surgically [3]. Because our patient presented a situation similar to that of the previous report, we attempted to determine whether an unidentified retained foreign body might be a metallic object or lipiodized oil. For perplexing cases which may not be apparent on conventional axial CT images, 3D-CT can offer many advantages in diagnosis and management of a retained foreign body [4]. Gemstone spectral imaging on single-source dual-energy CT can examine the relation between CT attenuation values and iodine concentration [5]-[7], which would appear applicable given the high iodine concentration of lipiodized oil. However, as neither resource offered conclusive evidence in our case, we describe continued limitations in demonstrating retained lipiodized oil in the abdominal cavity preoperatively using current medical equipments.

2. Case Report
A 33-year-old Japanese female with twins visited a local internal medicine clinic because of fever and epigastralgia in August 2014. Abdominal radiography taken at the clinic showed a high-density material measuring about 2 cm at the right floor side of the pelvis (Figure 1). Her children were delivered 6 years ago in 2008 at our hospital by Caesarian section due to premature rupture and breech presentation. No radiographs were obtained before or after that surgery because of extreme emergency, and she had not received any other operations. To clarify the unidentified foreign body, a CT scan was performed (Figure 2) showing a foreign body with density of 3053 Hounsfield Units (HU). The CT value was so high that we suspected the possibility of residual metallic material from the emergency operation. But, hospital files for the emergency operation did not record any missing instruments. On the other hand, we learned from the preoperative interview that the patient had undergone hysterosalpingography at a local obstetrics and gynecology clinic for an inspection of infertility before the pregnancy. Thus, we also considered the possibility of residual oil-based contrast media. A 3D-CT was performed to gain some clarity about the residual high-density material (Figure 3(a) and Figure 3(b)), but we could not identify any decisive evidence.
A laparoscopic surgery was performed to remove the material, because we could not rule out the possibility of metal and the patient requested the surgery. However, during the operation we did not find any metallic material in the pelvis. Therefore, we tried to locate the unidentified foreign body using X-ray imaging equipment. We found it below the peritoneum of the right floor side of the pelvis. The foreign body was a soft cyst of approximately 2 cm, and it was removed without injury (Figure 4). The cyst showed high density on radiography and contained a yellowish oily fluid. The fluid was sent to the School of Pharmaceutical Sciences, Graduate School of Biomedical Sciences, Nagasaki University and was shown to be very similar to the lipiodized oil.

After this operation, we were able to confirm from the doctor in charge at the local obstetrics and gynecology clinic that the lipiodol was used for hysterosalpingography.

3. Discussion

Hysterosalpingography is used commonly in the evaluation of infertility and in the diagnosis of anomalies of the uterus and fallopian tubes [8]. Lipiodized oil is an iodinated oil developed in 1922 that is widely used for hysterosalpingography. Oil-based contrast media such as lipiodol is thought to cause less discomfort to the patient, reduce the risk of pelvic infection, and be more effective at promoting fertility [9] [10]. Lipiodized oil is usually secreted via the lymphatic system within a few months, and prolonged retention over years is rare; however, retention appears to have been years-long in the report of misdiagnosis as residual metallic material [3]. Yet in investigating the current state of preoperative resources for our case, the 3D-CT image did not offer any suggestion as to the type of material contained in the high-density foreign body. As with the previous reported case, we
could not perform Magnetic resonance imaging (MRI) because of the possibility that the material might be a metallic object. A clear result from our attempts by 3D-CT or some other means might have helped avoid performing an unnecessary operation, as our patients had no symptoms due to the foreign body.

Postoperatively, we attempted an experiment to discriminate by gemstone spectral imaging on single-source dual-energy CT in another facility: lipiodol contains iodine, and spectral CT imaging can provide correct registration of data sets for conduction of accurate iodine-based material decomposition images [5]-[7]. However, there were no clear means of distinction. Our reasoning for this experiment was that a CT value obtained by conventional single-source CT system could have greater uncertainty because of the beam hardening effect. A CT value over 1000 HU is unreliable and inconsistent [3]. Therefore, the CT value of 3053 HU preoperatively by conventional CT system might not have been reflective of the accurate value, and there is a possibility that the actual value was considerably higher. In other words, the diagnostic difficulty in our case might have been related to inapplicability of non-CT diagnostics combined with CT limitations at very high HU, even by 3D or by spectral imaging, where the highest reported HU value for a range of iodine concentrations was below 2700 [5].

4. Conclusion

It is quite difficult to demonstrate retained lipiodized oil in the abdominal cavity preoperatively by the latest medical equipment. And, in our case, we should have conducted abdominal radiography immediately after Caesarian section. Had we done so, we may have prevented an operation at this time. This case highlighted the importance of a detailed preoperative interview concerning hysterosalpingography. However, we especially hope for the further progress of image analysis equipment especially for high Hounsfield Unit materials to help avoid unnecessary surgery.

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Conflict of Interest

The authors state that they have no Conflict of Interest (COI).

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Chronic Urticaria Due to Allergy to Wheat Alpha-Amylase Inhibitor Proteins

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Abstract

Chronic spontaneous urticaria (CSU) is defined as the spontaneous appearance of wheals, angioedema, or both, for at least 6 weeks, due to known or unknown causes [1]. In some patients who present a CSU with daily or almost daily symptoms a type I allergy could be the underlying cause. We present one adult patient with chronic urticaria who was finally diagnosed as a non-occupational case of IgE-mediated wheat allergy manifested following exposure by 3 different routes: inhalation (rhinitis and bronchial asthma), dermal absorption (contact urticaria) and ingestion (systemic chronic urticaria). We were able to detect the culprit proteins by immunoblotting. Serum IgE binds mainly to alpha-amylase/trypsin inhibitors and, to a lesser extent, to other proteins associated with food allergy to grains (e.g. beta-glucanase, serpin, peroxidase). In our opinion, skin prick tests with a food standard battery could help in the etiological diagnosis of chronic urticaria. The identification of responsible allergens could be difficult because only a few complex in vitro techniques allow detecting the allergy to several proteins.

Keywords

Alpha-Amylase Inhibitor, Wheat, Chronic Urticaria, Allergy

1. Introduction

Hypersensitivity reactions following cereal intake can be IgE-mediated or not (e.g. celiac disease). There are cases, however, of celiac disease associated with IgE-mediated allergy to cereals [2]. IgE-mediated reactions can occur by inhalation (e.g. Baker’s asthma and rhinitis), ingestion (e.g. gastrointestinal manifestations [3], chronic urticaria) and skin absorption (e.g. contact urticaria).

A few prevalence studies of food allergy to cereals have been reported. This sensitization tends to disappear.
with age, being rare in adults, in whom could cause the exacerbation of atopic dermatitis [4].

The aim of this paper is to present a case of chronic urticaria which was resolved by avoiding the causative agent, in this case, cereals.

2. Case Report

A 29-year-old woman, with no relevant medical or surgical history, had had very pruritic generalized urticaria and occasional angioedema for 1 year. Urticarial lesions appeared daily, especially in the morning when she ate bread at breakfast, and partially improved with antihistamines. Since childhood, she had rhinoconjunctivitis and asthma in places where cereal flour was handled, and contact urticaria when she kneaded bread at home.

The allergy study included skin prick test with a food standard battery, flours and foods containing cereals, measurement of total and specific IgE (CAP, Thermofisher®; ISAC microarray), and SDS-PAGE immunoblotting (in reducing and non-reducing conditions of electrophoresis). Positive results were obtained with flour mixture, gliadin, wheat, barley, rye and corn, whereas prick by prick with oat and different foods containing cereals (e.g. Coca-Cola®, cacao drink, soluble cereals) [5] were negative. Total IgE was 331 kUA/l. Specific IgE results were positive with barley (61.8 kUA/l), rye (50.3 kUA/l), wheat (6.99 kUA/l) and gluten (3.48 kUA/l), and negative (<0.35 kUA/l) with rice, corn, α5-gliadin and rPru p3. Tri a 14 (LTP), Tri a 19 (α5-gliadin), nTria aATI (trypsin inhibitor) and buckwheat (2S albumin) analysed with the ISAC microarray system were also negative.

SDS-PAGE immunoblotting performed with wheat, barley, rye, oat, rice, corn and gluten, showed low molecular weight IgE binding bands (around 14 kDa). As shown in Figure 1 (immunoblot with electrophoresis done under non-reducing conditions), the bands in the samples of wheat, barley, rye, oat, and gluten, may represent α-amylase/trypsin inhibitor family proteins.

Negative anti-tissue transglutaminase autoantibodies and normal immunoglobulin count were detected in blood analysis.

The patient tolerated oral food challenge with rice and corn, being diagnosed of contact and chronic urticaria, and rhinitis and bronchial asthma due to allergy to wheat α-amylase inhibitor. The symptoms had been resolved without receiving any treatment, after avoiding the ingestion of cereals (wheat, barley, rye and oat) for 15 days. We allowed rice and corn intake due to the good tolerance demonstrated in the controlled oral challenge.

3. Discussion

Gramineae family members are distributed in different subfamilies. The Pooidae subfamily includes Triticeae (wheat, rye, barley) and Aveneae (oat) tribes. Certain cross-reactivity has been described between members of the Triticeae tribe [6], but there are different patterns of clinical tolerance.

Figure 1. Immunoblot with electrophoresis performed under non-reducing conditions with seeds (wheat, barley, rye and oats) and extracts (rice, corn and gluten).
The cereal grain proteins may act as allergens in cereal flour and according to their solubility in different solvents can be grouped into different protein fractions: albumin, globulin and gluten proteins (prolamins and gliadins) [7]. These proteins have different biological functions, such as storage, metabolic, structural and defense [8].

Most salt-soluble proteins are enzymes and enzyme inhibitors, whereas the salt-insoluble (e.g. gluten proteins) are usually seed storage proteins and constitute 80% of the protein fraction of cereal grain. Many of these proteins (gluten, enzymes, enzyme inhibitors, surface proteins) act as the major allergens in Baker’s asthma and food allergy to cereals (e.g. alpha-amylase/trypsin inhibitors, LTP, serpin).

Within the prevalence studies of food allergy to cereals, there is an observational study carried out in Spain (Alergológica 2005), in which cereals represented only 3.3% of all food allergens [9]. There are few reports of chronic urticaria due to wheat intake. Kanny et al. described an adult with chronic urticaria and asthma due to allergy to wheat flour (based on specific IgE to wheat flour and positive oral challenge test) [10]. Mingomataj et al. diagnosed allergy to alpha-gliadin by a positive prick test in another adult who showed chronic urticaria, headache, arthralgia and amenorrhea. Their symptoms resolved after a gluten-free diet [11].

Our patient was sensitized to wheat alpha-amylase inhibitors, which have a defensive role against digestive alpha-amylases of different parasites. They come from the grain endosperm and are present in all wheat protein fractions (albumins, globulins, gliadins, glutenins) [12]. They are salt soluble proteins and their molecular mass is around 12 - 16 kDa. There are 11 allergenic proteins belonging to this family that may cause allergy by inhalation and/or ingestion (those being major allergens in Baker’s asthma and wheat food allergy in children and adults) [7] [13]. The reactions by ingestion are often associated with exercise or atopic dermatitis.

As the main route of sensitization to flour is inhalatory, our patient could be sensitized in childhood and adolescence manipulating raw flour daily for making homemade bread, manifesting asthma and rhinitis, and later developing a food allergy in the form of urticaria that can be regarded as chronic (given that it lasted for longer than 6 weeks).

4. Conclusions

We consider this case of interest as our patient is an adult with IgE-mediated allergy to wheat manifested following exposure by 3 different routes: inhalation (rhinitis and bronchial asthma), dermal absorption (contact urticaria) and ingestion (systemic chronic urticaria). We were able to detect the culprit proteins by immunoblotting. Serum IgE binds mainly to alpha-amylase/trypsin inhibitors and, to a lesser extent, to other proteins related to food allergy by grains (e.g. beta-glucanase, serpin, peroxidase).

The study of patients with chronic urticaria should include screening for a food allergy because it may be helpful in rare instances as in our case. The actual prevalence of the sensitization to the alpha-amylase/trypsin inhibitor proteins in cereal allergy is unknown in part because there are only a few complex in vitro techniques that allow its detection.

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Competing Interests

The authors declare that they have no conflicts of interest. ISAC microarray and SDS-PAGE immunoblotting techniques were carried out with the help from Dr. Borja Bartolomé, director of the applications laboratory of the pharmaceutical company Bial-Aristegui.

Authors’ Contributions

All authors have been involved in drafting the manuscript and revising it critically, giving final approval of the version to be published.

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Oral Pathergy in Sweet’s Syndrome Following Food Bolus Injury

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Abstract

Pathergy is a unique and dramatic clinical finding of exuberant inflammation in response to local trauma. This incompletely understood phenomenon presents with sterile pustules and ulcers after minor cuts or scrapes, and can be tested by a pricking the skin with a sterile needle. Historically, pathergy was thought to be pathognomonic for Behcet’s syndrome, though it has also been described in several other inflammatory conditions such as pyoderma gangrenosum and acute febrile neutrophilic dermatosis (Sweet’s syndrome). Recognizing Sweet’s syndrome specifically can be challenging due to its atypical clinical course, and understanding the relationship between Sweet’s syndrome and pathergy can offer an important diagnostic clue. We present a case of Sweet’s syndrome presenting with upper airway obstruction and pathergy. To our knowledge, this is the first documented case of Sweet’s syndrome presenting with oral pathergy.

Keywords

Pathergy, Sweet’s Syndrome, Myelodysplastic Syndrome, Neutrophilic Dermatosis

1. Introduction

Sweet’s syndrome, or acute febrile neutrophilic dermatosis, is a rare, poorly understood systemic inflammatory disorder. Originally described in 1964 by Dr. Robert Sweet, this syndrome presents with abrupt onset of erythematous or hemorrhagic rash with skin biopsy showing neutrophilic invasion of the dermis without leukocytoclastic vasculitis [1]. The presences of fever, leukocytosis, elevated inflammatory markers, and rapid resolution with prednisone are also diagnostic characteristics [Table 1]. Most cases are idiopathic, but a significant percent are either drug induced (most commonly granulocyte colony stimulating factor) or paraneoplastic (solid organ or hematologic) [2]. The pathergy phenomenon has also been associated with Sweet’s syndrome, most often associated with the paraneoplastic subtype. We present the case of a 68 years old female who presented to the hospital with upper airway obstruction from pathergy and was found to have Sweet’s syndrome.
Table 1. Diagnostic criteria for Sweet’s syndrome. The presence of both major and two minor criteria are required.

| Major criteria                                                                 | Minor criteria                                               |
|-------------------------------------------------------------------------------|--------------------------------------------------------------|
| Abrupt onset of characteristic rash (papules and nodules)                     | Fever > 38 degrees Celsius                                    |
| Biopsy proven dermal infiltration of neutrophils without vasculitis          | Association with malignancy or inflammatory syndrome         |
| Excellent response to glucocorticoids                                          | Elevated inflammatory markers on presentation (3 of 4)       |
|                                                                                                                                 |
| • ESR > 20 mm/h                                                               | • Positive C-reactive protein                                |
| • Leukocyte count > 10,000/ul                                                  | • Over 70% neutrophils                                       |

Source: Malone et al., Arch Dermatol. 2002; 138(3): 345-349. doi:10.1001/archderm.138.3.345.

2. Case Report

A 68 years old Asian female with a past medical history of transfusion dependent myelodysplastic syndrome (MDS) presented with airway obstruction from acute oropharyngeal swelling. The patient was emergently nasally intubated for airway protection and was therefore unable to give a history, but per her family she experienced 5 days of fever, oral pain, and facial edema prior to admission. She was febrile to 39.1 degrees Celsius, tachycardic to 147 beats per minute, and mildly hypertensive to 144/87 mmHg. Physical exam showed a diffusely edematous oropharynx and tongue with scant hemorrhagic bullae. The remainder of her physical exam was normal. Her CBC, BMP and inflammatory markers are shown on Table 2.

CT soft tissue neck revealed a 2.7 × 1.4 × 3.8 cm mass along the R palate and R neck. Vancomycin, clindamycin, and meropenem were started empirically, along with IV dexamethasone 4 mg q6h. Biopsy of the oral process showed inflammation with necrosis and hemorrhage, but no neoplasia. Blood and tissue cultures were negative. An autoimmune workup was performed and was negative for lupus, mixed connective tissue disease, rheumatoid arthritis, Sjogrens, vasculitis, or hereditary angioedema [Table 3].

The patient’s swelling & fever improved and she was extubated hospital day four, and steroids were tapered off. Two days later, she developed recurrent fevers, oral pain and swelling. Repeat blood cultures were negative, and buccal biopsy staining and culture showed no bacteria, AFB, fungus, or neoplasm. Microscopy of the buccal mass tissue was again consistent only with chronic and acute hemorrhage with scattered mast cells and neutrophils. The return of fever after discontinuation of glucocorticoids, superimposed on the continuation of antibiotics is shown on Figure 1.

Three days after the removal of glucocorticoids, the patient developed painful erythematous plaques on her trunk and also induration of the right forearm concerning for necrotizing fasciitis [Figure 2]. Surgical exploration of the arm was negative for signs of infection, but over the course of the next 12 hours the site of surgical trauma developed a sheet of coalescent pustules consistent with a pathergy response [Figure 3]. Punch biopsy of a trunk lesion showed a superficial, thin band of neutrophils with sparing of the epidermis and intact endothelium of the blood vessels consistent with neutrophilic dermatitis. Sweet’s syndrome was diagnosed based on the constellation of biopsy findings, pathergy phenomenon and negative pathology and microbiology in a patient with underlying MDS. Prednisone 60 mg/d was started and within several days her fever and cutaneous lesions resolved, and she experienced dramatic global improvement. While the specific cause of the patient’s initial upper airway obstruction is unknown, she attested to oral trauma from a food bolus the day her symptoms started. It is probable that this represented oral pathergy.

3. Discussion

Diagnosis and Treatment

This patient originally presented with upper airway obstruction, which was later found to be the initial symptom
Table 2. Admission complete blood count, basic metabolic panel, and inflammatory markers. The thrombocytopenia was baseline for the patient due to her MDS.

| Complete blood count |     |
|----------------------|-----|
| WBC                  | \(4.1 \times 10^3\) |
| RBC                  | \(3.5 \times 10^3\) |
| HGB                  | 9.8 |
| HCT                  | 28.9 |
| Platelets            | \(<10 \times 10^3\) |
| Segs (%)             | 53% |
| Blasts (%)           | 7%  |

Basic metabolic panel

| Glucose   | 178 mg/dl |
| BUN       | 13 mg/dl  |
| Creatinine| 0.3 mg/dl |
| Sodium    | 138 mEq/L |
| Potassium | 4.1 mEq/L |
| Chloride  | 106 mEq/L |
| CO2       | 21 mEq/L  |

Table 3. Inflammatory and autoimmune panels.

| Sedimentation rate | 108 mm/hr |
| C reactive protein | 26.8 mg/dl |
| ANA screen         | Negative  |
| DS DNA screen      | Negative  |
| ENA Smith          | Negative  |
| ENA RNP            | Negative  |
| Rheumatoid factor  | Negative  |
| SS A antibody      | Negative  |
| SS B antibody      | Negative  |
| C-ANCA             | <1:20      |
| P-ANCA             | <1:20      |
| C1 esterase inhibitor | 39 (within normal limits) |
| C3 complement      | 103 (within normal limits) |
| C4 complement      | 25 (within normal limits) |
Table 1. Summary of medications and dosages.

| Hospital Day | 00-06 | 08-16 | 16-00 | 00-06 | 08-16 | 16-00 | 00-06 | 08-16 |
|--------------|-------|-------|-------|-------|-------|-------|-------|-------|
| Temperature  |       |       |       |       |       |       |       |       |
| Steroids     |       |       |       |       |       |       |       |       |
| Dexamethasone | 10    | 10    | 10    | 20    |       |       |       |       |
| Anti-Infectives |     |       |       |       |       |       |       |       |
| Acyclovir Capsules |       |       |       |       |       |       |       |       |
| Acyclovir Solution |       |       |       |       |       |       |       |       |
| Clindamycin | 600 mg/50 mL | 600 mg/50 mL | 600 mg/50 mL | 600 mg/50 mL | 600 mg/50 mL | 600 mg/50 mL | 600 mg/50 mL | 600 mg/50 mL |
| Meropenem | 1 g | 1 g | 1 g | 1 g | 1 g | 1 g | 1 g | 1 g |
| Micafungin | 500 mg | 500 mg | 500 mg | 500 mg | 1,000 mg | 500 mg | 500 mg | 500 mg |
| Vancomycin | 500 mg | 500 mg | 500 mg | 500 mg | 500 mg | 500 mg | 500 mg | 500 mg |

**Figure 1.** Return of previously treated fever with discontinuation of glucocorticoids.

**Figure 2.** Patient’s right arm, immediately preop.

**Figure 3.** Patient’s right arm, 12 hours postop.
of Sweet’s syndrome. At the time of presentation, there was no history of oral trauma, which made identifying the oral lesion a possible pathergy response diagnostically impossible. It was only after the patient developed pathergy to her surgical incision that the diagnosis became clear. With subsequent skin biopsy positive for neutrophilic infiltrate without leukocytoclastic vasculitis, characteristic truncal rash, hematologic malignancy, fever, and resolution of symptoms with glucocorticoids, she fit both major and three out of four minor criteria for Sweet’s.

Sweet’s syndrome can present with a variety of clinical phenomena that are not a part of its diagnostic criteria of inflammation and a papular/nodular rash. Solid organ involvement has been seen including encephalitis [3] myocarditis, hepatitis, glomerulonephritis [4], and sterile osteomyelitis. Bullous Sweet’s [5], subcutaneous Sweet’s, and neutrophilic dermatosis of the dorsal hands [6] are common variants that present with atypical rash patterns. Nonspecific symptoms related to systemic inflammation such as malaise and diffuse pain are also commonly reported. Pathergy is uncommonly documented in Sweet’s, but has a known association.

The pathergy response can be seen in a number of disorders, most notably Behcet’s syndrome, where an inflammatory response to pinprick injury is part of the diagnostic criteria [7]. The response can be exuberant, and is often stimulated in response to minor or unnoticed trauma. While pathergy is not needed to diagnose Sweet’s, it can offer a crucial clue as it did in this case. A detailed literature review found one other documented case of airway obstruction caused by pathergy in Sweet’s syndrome, though in that case the inciting trauma was from a biopsy needle [8].

We chose to treat the patient with prednisone 60 mg/d. Prednisone 0.5 - 1 mg/kg/d is the standard dosing protocol for Sweet’s syndrome to be continued for at least 4 - 6 weeks [9]. While colchicine and dapsone have also been shown anecdotally to be effective therapies, systemic glucocorticoids remain the gold standard. Success is assessed by rapid (<48 hours) resolution of fever and painful rash [10].

4. Conclusion

Making an initial diagnosis of Sweet’s syndrome can be difficult due to its somewhat ambiguous presentation of systemic inflammation and rash, as well as the need for a skin biopsy. Without a very high index of suspicion, diagnosis can often be delayed resulting in patient morbidity. It is important for clinicians to recognize pathergy as a sign of Sweet’s syndrome, and pursue a skin biopsy if new pathergy is observed in a patient with unexplained systemic inflammation. This is the first documented case of Sweet’s syndrome presenting with oral pathergy.

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Left Ventricular “Horseshoe-Thrombus”—A Case Report

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Abstract

Thrombi represent the most frequently found intracardiac masses. Left ventricular thrombus (LVT) is an important complication in patients with ischemic heart diseases and in those with dilated cardiomyopathy and systolic heart failure. The diagnosis of left ventricular thrombus remains important since anticoagulation will reduce the risk of systemic embolization and stroke. Despite advances in other imaging modalities, echocardiography remains the most important tool for diagnosis and risk stratification in patients predisposed to develop left ventricular thrombi. Mural thrombi formed on the left ventricular endocardium and horseshoe-shaped in chronic dilated cardiomyopathy, masquerading as left ventricular endomyocardial fibrosis was diagnosed by transthoracic 2D echocardiographic imaging in a 38 years old middle aged man. Background of this case highlighted the pathophysiology, high risk echocardiographic features and the role of anticoagulant therapy in LV thrombus with dilated cardiomyopathy.

Keywords
Thrombus, Left Ventricle, Dilated Cardiomyopathy, Echocardiography, Anticoagulant Therapy

1. Introduction

Thrombus is defined as a discrete echo dense mass with defined margin, distinct from the endocardium and seen throughout systole and diastole. Intracardiac thrombi are classified as left ventricular, left atrial, right sided and valvular thrombi. Left ventricular thrombi are typically located in areas of severe wall motion abnormalities.

The pathophysiologic mechanism for left ventricular thrombus (LVT) formation in the so-called “Virchow’s triad” was postulated in patients with acute myocardial infarction or in those with dilated cardiomyopathy and congestive heart failure. The triad consists of stasis of blood, endothelial injury or dysfunction and a hypercoagulable state. LV regional wall akinesia and dyskinesia result in blood stasis; prolonged ischemia leads to sub-
endocardial tissue injury with inflammatory changes and a hypercoagulable state. Thus the combination of blood stasis, endothelial injury and hypercoagulability, often referred to as Virchow’s triad, is a prerequisite for in vivo thrombus, composed of fibrin, red blood cells, and platelets. Thrombi occupying in heart chambers are designated as mural thrombi. Abnormal myocardial contraction or endocardial injury promotes cardiac mural thrombi formation. In patients with dilated cardiomyopathy, low-velocity swirling of blood within the left ventricle also predisposes to the development of a thrombus due to altered hemodynamics associated with poor myocardial contractility. Thrombi may undergo propagation, embolization and dissolution. The older thrombi become organized by the growth of endothelial cells, smooth muscle cells and fibroblasts. Eventually, with remodeling and contraction of the mesenchymal elements, only a fibrous lump may remain to mark the original thrombus. The fibroed thrombi may undergo hyalinization and calcification.

It has been speculated that LV thrombus provides a positive role by offering mechanical support to the myocardium and therefore protecting against LV rupture. The thrombus becomes firmly attached to its site of origin, enhancing the underlying myocardial scar, partially restoring the thickness of the myocardial wall and limiting the potential of its expansion.

A chronic fibroed organized thrombi visible as horseshoe-shaped in LV cavity around the apex in chronic dilated cardiomyopathy is uncommon and so this case had been reported.

2. Case Report

A 38 years old middle aged man, having frequent episodes of bronchial asthma for one year duration was referred to this hospital for echocardiography. His pulse rate was 116 bpm and blood pressure 110/70 mmHg. Physical examination revealed normal JVP (Jugular Venous Pressure), enlarged apical impulse, muffled heart sounds and no murmur. Lung fields revealed basal rales and rhonchi. Blood chemistry revealed no abnormalities. ECG was normal. X-ray chest revealed cardiomegaly. Transthoracic 2D echocardiography revealed dilated cardiomyopathy with a measured ejection fraction of 23% and a chronic, laminar, flat, fibroed, organized, large horseshoe-shaped thrombus occupying the apex and adjacent portion of LV (left ventricular) cavity as shown in Figure 1, Figure 2 and Figure 3. Figure 1 revealed the horseshoe-shaped thrombus around the LV apex in apical four chamber view. Figure 2 revealed its maximal thickness of 18 mm in tilted two chamber view, Figure 3 revealed the thrombus embedded along the papillary muscle and a dilated LV cavity of 68mm in parasternal long axis view. Color Doppler showed no regurgitant lesions across the AV valves and both mitral and tricuspid leaflets appeared normal.

![Figure 1](image1.png)

**Figure 1.** Apical four chamber view showing the horseshoe-shaped thrombus and dilated cardiac chambers suggesting dilated cardiomyopathy.
He was treated with antibiotics, bronchodilators and anti-failure measures. He was given a short course of warfarin therapy for one month and no change in the thrombus was observed. Since he developed one or two episodes of mild hemoptysis, warfarin therapy was withdrawn. He developed no embolic events on further follow up of 3 months without warfarin therapy. He died due to acute respiratory failure following a severe asthmatic episode.

3. Discussion

3.1. Frequency

Previously, the incidence of left ventricular thrombus (LVT) was reported to be as high as 30% - 40% in patients with an anterior wall myocardial infarction. For patients with an non-anterior myocardial infarction, the risk of LVT was lower (<5%) [1]. Although controversial, in the contemporary era of routine early revascularization and more aggressive anticoagulation, the incidence of LVT complicating an anterior myocardial AMI (acute myocardial infarction) is likely reduced and is currently estimated at 5% - 15% [2]-[4]. In patients with dilated
cardiomyopathy and congestive heart failure (CHF), the reported frequency of LVT varies from 10% - 30%, depending on the series [5] [6].

3.2. General Features

Thrombi are typically amorphous echogenic structures with varying shape and are adherent to the endocardium. Thrombi may be multiple, mobile and may protrude into the left ventricular cavity. In most cases, they have a texture and appearance that are distinct from the adjacent myocardium. Thrombi generally involve the apex of the left ventricle, most often in the presence of akinesis or dyskinesis. Predisposing factors include recent myocardial infarction, left ventricular aneurysm and dilated cardiomyopathy and thrombi can develop in any situation in which low flow and blood stasis occur.

Left ventricular thrombi (LVT) that complicate dilated cardiomyopathy (DCM) also are located more commonly at the apex, perhaps reflecting the propensity for left ventricular stasis, to be located further from the inflow and outflow tracts. Hypercoagulability and endothelial dysfunction also, are associated with DCM, fulfilling Virchow’s triad [7]. Unlike acute myocardial infarction, however, the development of LVT in patients with DCM is not marked by a distinct clinical event. This may account for the fact that most thrombi are found incidentally during echocardiographic assessment of left ventricular function or during evaluation of an embolic event.

Sometimes the thrombi may be flat lying along the left ventricular wall even in some cases, it may be very difficult to differentiate thrombus from myocardium. The distinction between thrombus and pannus formation is essential. Thrombi in general larger and have soft ultrasound density similar to myocardium, but pannus formation is usually more dense and small in appearance.

3.3. Echocardiography

Transthoracic echocardiography remains the most important imaging modality to make a diagnosis of left ventricular thrombus (LVT). Echocardiographic appearance of intracardiac thrombus is heterogenous, they can vary from a small, immobile mural thrombus to a large protruding mobile thrombi. Echodensity and shape of the thrombi depend on age and degree of thrombus organization. They may be homogenously echogenic or may have heterogenous texture with lucent areas. An echolucent center suggest that the thrombus is relatively new and actively growing. Very fresh thrombi tend to protrude into the center of the cavity and are highly mobile. Older thrombi generally have smooth cavitory surfaces and they are less likely to change or embolize. In some cases vascularization and layer formation can be found.

Transthoracic echocardiography has a sensitivity of 90% - 95% and a specificity of 85% - 95% for detection of LV Thrombus (LVT) in studies where the presence of thrombus was confirmed at surgery or autopsy [8] [9]. Echocardiographic criteria for LV Thrombus include:

- A distinct echogenic mass within the LV cavity (may be sessile/layered or protruding/mobile) that is contiguous with, but acoustically distinct from the underlying endocardial surface. It is seen throughout the cardiac cycle and visualized on at least two orthogonal views.
- An associated underlying region of severe wall motion abnormality, usually severe hypokinesis, akinesis, dyskinesis or aneurysmal dilatation.

Echocardiographically, left ventricular thrombus was defined as a discrete mass of echoes in the left ventricle that was distinct from the endocardium and seen in both systole and diastole, located in an area of asynnergy, and identified in at least two views. Given the propensity for thrombi to form at the apex of the left ventricle, the best imaging planes to visualize LV thrombus are apical views, where the transducer is closest to the region of interest. The characteristics of the thrombus, including intracavitary motion, shape (protruding vs flat), echodensity, heterogeneity and central lucency as defined by Haugland, et al. [10] have been described. The shape of thrombus may be protruding or flat. Thrombi that projected into the ventricular cavity were classified as protruding and thrombi that did not were classified as flat. A thrombus has usually an echodensity similar to the myocardium while pannus appears more hyperechoic [11]. Figure 1 illustrates a large, organized, immobile, fibrosed and calcified thrombus which is flat along the endocardium of apical LV cavity and visible as horseshoe-shaped in apical four chamber view of Transthoracic 2D echocardiographic imaging. An estimate of thrombus size, a one-dimensional measurement of maximal thrombus thickness was made perpendicular to the myocardium from the epicardial-pericardial interface to the innermost border of the thrombus-blood interface [12].
**Figure 2** illustrates the maximal thrombus thickness of 18 mm in Tilted two chamber view. Certain normal anatomic structures (papillary muscle, false tendon, trabeculations) and technical artifacts (reverberation, near-field artifacts) will result in false positive diagnosis of LVT [13]. **Figure 3** illustrates the tip of thrombus embedded along the papillary muscle in parasternal long axis view and a LV cavity dilation of 68 mm suggesting the dilated cardiomyopathy as a high risk factor for its development. High risk echocardiographic features for the development of LVT are shown in **Table 1** given below.

In this patient severe global LV systolic dysfunction with a measured ejection fraction of 23% and LV dilatation of 68 mm were the echocardiographic risk factors for the development of LV Thrombus.

LV Thrombus may masquerade the conditions such as EMF (Endomyocardial fibrosis) and other cardiomyopathy syndromes with similar pathologies. Endomyocardial fibrosis is a “vanishing mystery” in the coastal districts of South India and the Kerala state was once “the hot spot” for this enigmatic disease [14], sub-endocardial fibrosis affecting the apices and the inflow tract of the right or left ventricle or both define the disease [15]. It is characterized by apical obliteration, valvular regurgitation especially the posterior leaflets of mitral or tricuspid valves, atrial dilation with features of restrictive physiology and the disease came to be known as “Davie’s disease” [16].

A pedunculated thrombus in the left ventricular apex was visualized by the apical four chamber view of Transthoracic 2D echocardiography in dilated cardiomyopathy [17]. In the literature, there are two reports concerning the echocardiographic evidence of an intraventricular thrombus. Levisman et al. described the echocardiographic appearance of a pedunculated tumor in the left ventricle, which proved to be an organized thrombus [18]. De Joseph, et al. reported the echocardiographic findings in a patient with a large left ventricular thrombus [19]. In this patient, a large, flat, fibrosed, organized and calcified thrombus was visualized as horseshoe-shaped in apical four chamber, tilted two chamber and parasternal long axis views of 2D echocardiography in a 38 years old middle aged male with dilated cardiomyopathy.

### 3.4. Embolic Risk

Several studies have suggested that LV Thrombus that protrude into the ventricular cavity or that exhibit independent mobility are associated with a high risk of embolization. In dilated cardiomyopathy, the mechanism of embolization of LVT is less clear and several studies failing to demonstrate an increased risk of future embolization [20].

### 3.5. Anticoagulation Therapy

In patients with cardiomyopathy, the incidence of LV thrombus has been reported in the literature as 11% - 44% [21]. The definite treatment of LV thrombus is controversial. The main treatment options include thrombectomy, anticoagulation, and thrombolysis [22] [23].

Chronic oral anticoagulation has not been shown to decrease the risk of ischemic stroke or mortality in patients with LV dysfunction [24]. Anticoagulation should be individualized and considered in patients with a history of thromboembolic events, atrial fibrillation or evidence of an LV Thrombus. The level of anticoagulation

| S. No | High risk echocardiographic features for the development of LVT |
|-------|---------------------------------------------------------------|
| 1     | Large infarct size and extent                                 |
| 2     | Anterior myocardial infarction >> inferior infarction         |
| 3     | Severe global and regional LV systolic dysfunction, presence of CHF |
| 4     | Elevated LV end-systolic volume, LV dilatation               |
| 5     | Spontaneous echo contrast                                    |
| 6     | Abnormal flow pattern within the LV                          |
| 7     | Apical rotating flow                                         |
| 8     | Vortex ring formation                                        |
recommended varies but is generally targeted to an International Normalized Ratio (INR) of 2.0 to 3.0.

Similar to the post-myocardial infarction patient, a documented LVT in the setting of congestive heart failure and dilated cardiomyopathy likely warrants anticoagulation, especially if embolic potential is high and bleeding risk is low. Currently, no evidence exists for anticoagulation of chronic, layered, organized, mural thrombi. Due to the current lack of definitive studies, the primary prevention of cardio-embolic stroke through therapeutic anticoagulation remains controversial in patients with dilated cardiomyopathy and congestive heart failure. Despite the lack of supportive data, given that the greatest benefit would be expected for those with severe LV dysfunction (LVEF < 20%) or a previous history of an embolic event, the use of anticoagulation in this select patient population may be reasonable [25].

In this patient, LV dilation of 68 mm with a LVEF of 23% and a documented LV Thrombus may suggest the use of anticoagulation is reasonable. Since the LV Thrombus in this case is a chronic, fibrosed, organized with calcification and densely adherent to the endocardium of LV apical region as a protective layer to limits its expansion and rupture, the benefit of anticoagulation is questionable. The patient may not experienced any embolic events previously and so the chronic anticoagulation therapy is not preferred in this case further after a trial of warfarin therapy for one month period.

4. Conclusion

Left ventricular thrombi in chronic dilated cardiomyopathy, visible as horseshoe-shaped, was detected by trans-thoracic 2D echocardiographic imaging. It is an interesting feature masquerading as endomyocardial fibrosis in a 38 years old middle aged man in coastal districts of South India at Thoothukudi region in Tamil Nadu state.

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Duodenal Perforation Caused by Distal Migration of Biliary Stent

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Abstract

Background: Migration of endoscopically placed biliary stents is a known complication of endoscopic retrograde cholangiopancreatography, which has a reported incidence of 3% - 6%. Usually, distal migration is asymptomatic and is detected incidentally. Case Presentation: We present a rare case of duodenal perforation caused by distal migration of a biliary stent. A 50 years old gentleman initially presented with cholangitis. ERCP showed a dilated common bile duct with a 9 mm stone and a biliary stent was placed. The patient subsequently presented with biliary peritonitis due to the migration of the stent causing perforation of the anterior wall of the second part of the duodenum. Emergency laparotomy was performed to remove the stent and the perforation was repaired. The patient made an uneventful recovery. Discussion: A brief discussion on stent migration is also conducted. Whilst distal migration of stents is less common than its proximal counterpart, it is important to note that rare complications may arise and be addressed in a timely manner.

Keywords

Cholangiopancreatography, Endoscopic Retrograde, Cholangitis, Intestinal Perforation

1. Introduction

Endoscopic biliary stent insertion is a well-established treatment of choice for relieving obstructive jaundice in both benign diseases such as choledocholithiasis as well as unresectable hepatobiliary malignancy. However, it is not without complications which range between 8% to 10% [1]. Biliary stent specific complications include migration, occlusion and intestinal obstruction. In the majority of instances, stent migration is asymptomatic. Nevertheless, there are several sporadic reports of small bowel perforation, colonic diverticular perforation, co-
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Iatrogenic fistula and intra-abdominal abscess caused by biliary stent migrations in literature [2] [3]. Herein we present a case of duodenal perforation caused by the distal migration of a biliary stent. A brief discussion of proposed mechanism is also conducted.

2. Case Presentation

A 50 years old gentleman was admitted to our hospital for cholangitis. He presented with fever and right upper quadrant pain. Blood tests showed leukocytosis and deranged liver function in an obstructive pattern. Urgent ultrasonography of abdomen confirmed a dilated biliary tree and the presence of gallstones. Emergency endoscopic retrograde cholangiopancreatography (ERCP) was done which showed a dilated common bile duct (CBD) to 15 mm with a 9 mm stone in the distal common bile duct. A 10 French, 10 cm long plastic biliary stent was inserted for biliary drainage. He was discharged a few days later uneventfully and was planned for ERCP and removal of stones as well as interval cholecystectomy later.

However, he was readmitted 1 week after ERCP, complaining of severe abdominal pain. Abdominal examination revealed guarding at upper abdomen guarding at upper abdomen with rebound tenderness. The patient was tachycardic with a pulse of 140/min. His respiratory rate was 20/min. Laboratory investigations showed a white cell count of $23 \times 10^9/L$ and a bilirubin of 32 umol/L. Hemoglobin, ALP, ALT, AST, amylase and renal function tests were within normal limits. CXR showed free gas under the diaphragm.

Urgent abdominal computer tomography (CT) scan confirmed the presence of free gas and distal migration of the biliary stent causing perforation of the duodenum. Emergency laparotomy showed biliary peritonitis and the plastic stent was seen protruding from the anterior wall of the second part of the duodenum (Figure 1). The stent was removed, exploration of the common bile duct was performed together with a T-tube placement. The duodenal perforation was repaired, the perforation site was closed with an omental patch and an abdominal drain was placed next to the duodenal perforation.

The patient was put on total parental nutrition post-operatively for 3 weeks. A T-tube cholangiogram, performed two weeks post-operatively showed no leakage from the duodenum, with free passage of contrast down into the distal small bowel. The T-tube was clamped and the patient started on fluids and subsequently on a solid diet. The abdominal drain was removed 4 days after the patient resumed oral feeding. He was discharged 4 weeks after admission and the T-tube was removed 2 months post-operatively. Interval cholecystectomy was subsequently performed. The patient was followed up for two years during which time he had no further abdominal complaints.

3. Discussion

Endoscopic biliary stent insertion has been used for many years as a temporary or definitive treatment for biliary obstruction. Two commonly available stents are classified according to synthetic material, namely plastic and......
metallic stents. The majority of plastic stents are straight type with a slightly curved shaft and flaps near both ends to prevent proximal and distal migration. According to a retrospective review studying 378 biliary plastic stent insertions, 13.5% presented with either proximal or distal migration; 7.9% for proximal and 5.9% for distal migration respectively. All the patients with proximally migrated stent presented with cholangitis or recurrence of painless jaundice which required endoscopic retrieval of stents, while distally migrated stent patients were usually asymptomatic, and presented as an incidental finding on follow up ERCP [4].

Despite the relatively innocent behavior of distal stent migration, there are numerous rare complications reported in the literature, such as duodenal perforation, colonic perforation resulting in pelvic abscess, enterocutaneous fistula or necrotizing fascitis. Distal stent migration more commonly occurs in benign compared to malignant strictures. This is because benign stenosis would undergo regression once the inflammatory reaction has subsided like what has occurred in our patient, while malignant stenosis may grow further and can tightly anchor the stent in position. Other important risk factors for distal stent migration include inappropriate stent selection and stent placement. In other words, if too long a stent was chosen, or if there was malposition of stent with a long segment within the duodenal lumen. This could result in impaction of the duodenal wall and perforation of duodenum. Perforation of the duodenum can be intra-peritoneal resulting in biliary peritonitis or retroperitoneal causing a bilioma [5]. Besides the duodenum, other common sites of perforation are the diverticular sac of the large bowel, as the walls of the diverticula are extremely thin, or in fixed areas of the intestines because of adhesion from previous operations.

The treatment for distal stent migration is quite controversial. In cases of obvious peritonitis and unstable hemodynamics, immediate surgical exploration is warranted. In the literature, there was also reporting of endoscopic extraction of migrating stent and endoscopic clip closure of duodenal perforation [6]. In the case of retroperitoneal perforation and localized bilioma, successful percutaneous extraction of stent and drainage has been reported [7].

4. Conclusion

To conclude, distal stent migration is not innocent; it can cause potentially lethal complications as seen in our presented case. In order to prevent such complications from occurring, endoscopists should choose the correct size, length and shape of the biliary stent, and avoid prolonged placement of stent in benign biliary obstruction.

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A Rare Cause of Late-Onset Epilepsy: Linear Scleroderma en Coup de Sabre

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abstract

Late-Onset Epilepsy (LOE), with onset in adult life, is often attributed to cerebrovascular disease and intracranial tumor. Herein we present a LOE patient with history of Linear Scleroderma en Coup de Sabre (LScs) and abnormal cranial MRI signs. Curiously, his band-like skin lesion, presenting on the forehead, was in line with the surface projection of the intracranial focus shown in MRI. This gave a clue of the link between the skin lesion and the intracranial focus and the epilepsy. To sum up, it exposed a rare cause of LOE. Moreover, it underlined the significance of recognizing the cause to be associated with a substantially increased risk of developing epilepsy.

Keywords

Epilepsy, Late-Onset, Linear Scleroderma en Coup de Sabre

1. Introduction

Late-Onset Epilepsy (LOE), with onset in adult life, is often attributed to cerebrovascular disease and intracranial tumor [1]. While our patient indicated a rare cause, which is the Linear Scleroderma en Coup de Sabre (LScs). LScs, a special subtype of scleroderma, is a rare disorder characterized by a band-like region of dermal thickening and hardening restricted to the forehead, giving the resemblance of the skin lesion to the stroke of a sabre. Although it is generally regarded as an autoimmune disease, the definite etiology has never been convincingly established. LScs primarily affects the skin, and may also affect underlying tissue. So, neurologic symptoms are not infrequently to be seen [2], but the LOE is rare in LScs patients, especially with the ischemic foci shown in MRI.

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2. Case Report

A 33-year-old man presented with a band-like skin lesion on his forehead (Figure 1(A)), was brought to our emergency department with complains of epilepsy. According to witness, the seizure was presented with loss of consciousness and flickering of the right mouth angle. There was no uprolling of eyes, incontinence or tongue bite then. The seizure stopped in around 20 seconds and the patient regained consciousness. Another seizure attack occurred in emergency department with features of loss of consciousness, uprolled eyes and twisted extremities. There was no incontinence or tongue bite. The patient regained consciousness in about 2 minutes after promptly getting intravenous diazepam. Neurological examination showed no other definite abnormalities except anomic aphasia and depressed left nasolabial groove. The patient underwent an electroencephalograph (EEG) examination and continuous spikes, and spike and waves were reported in left temporal region for about 2 mins 30 secs. A Magnetic Resonance Imaging (MRI) scan of the brain was performed and abnormalities (Figure 1(B)-(D)) were revealed, which were just subjacent to the skin lesion of the scalp. This gave a clue of the link between the skin lesion and the intracranial foci and the epilepsy. According to the patient’s history, he was clinically diagnosed with Linear Scleroderma en Coup Sabre (LScs) at the age of 2, which was then a small reddish plaque on his left forehead. After admission, he underwent a biopsy specimen from the lesion area, and the findings (Figure 1(F)) were consistent with the histopathologic features of late fibrotic stage of LScs [3]. No previous similar case was reported in his family. Anticonvultery therapy was performed with levetiracetam 500 mg twice a day with current fairly good control of seizures.

Figure 1. (A) A typical band-like, slightly depressed, 9 cm × 4 cm indurated skin lesion (white arrow) overlying the left frontoparietal area was shown. It was hyperpigmented and associated with alopecia and hynesthesia, restricted to the forehead, and did not extend below the forehead; (B) Axial T2-weighted image showed left scalp atrophy (white arrow) with T2 hyperintensities in left semioval center (black arrow); (C) Axial fluid attenuated inversion recovery (FLAIR) image demonstrated left scalp atrophy (white arrow) with T2 hyperintensities in left semioval center (black arrow); (D) Coronal TI image demonstrated enlargement of left lateral ventricle and wider and deeper left lateral sulcus (gray arrow); (E) The left middle cerebral artery (MCA) shown in the magnetic resonance angiography (MRA) is slimmer (white arrow) compared to the right one, concurrent with the decreased distal vessels; (F) The biopsy specimen from the lesion area demonstrated that the upper 1/3 of dermis was filled with tightly packed collagen fibers associated with cuticles and adnexal structures. Fat cells in the subcutaneous tissue were replaced by collagen. Small sweat glands were atrophic and surrounded by thickened collagen bundles.
3. Discussion

Scleroderma encompasses a wide range of diseases from diffuse (Systemic Scleroderma, SS) to localized (Localized Scleroderma, LS) cutaneous fibrosis presentation, which is characterized by dermal thickening and hardening due to increased collagen deposition. Visceral fibrosis is visible in SS but not in LS. When the lesion of LS is restricted to the forehead given the resemblance of the skin lesions to the stroke of a sabre, it is referred as Linear Scleroderma en Coup de Sabre (LScs) [4]. LScs usually occurs in the first or second decades of life, and predominantly affects females. It slowly progresses for 2 to 5 years, preceded by stable period. Although it is generally regarded as an autoimmune disease, the definite etiology has never been convincingly established. LScs primarily affects the skin, and may also affect underlying tissue. So, neurologic symptoms are not infrequently to be seen, notably pediatric epilepsy [5], with subcortical calcification as the most common MRI sign [2].

To the best of our knowledge, the LOE is rare in LScs patients, especially with the ischemic foci shown in MRI. According to the previous reports, ischemic foci was not the main sign of cranial MRI, only that Kanzato N reported a localized scleroderma case in 1999, in which one the progressing ischemic stroke was associated and autoimmune pathogenesis of cerebrovascular injury was postulated as the possible reason [6]. For the sake of approaching the reason of the ischemic foci in our case, a Magnetic Resonance Angiography (MRA) was performed with scarcity of typical change of vasculities to stand by the immunological hypothesis although it seems to be the most generally accepted one by now. But we noticed that the left Middle Cerebral Artery (MCA) shown in the MRA is slimmer (Figure 1(E)) compared to the right hemisphere, concurrent with the decreased distal vessels. Taken together, the hypothesis which seems to be capable of coincidently interpreting both the cerebral atrophy and the slimmer vessels is a distinct one [7], which believes in that an early defect affecting one side of the rostral neural tube can cause facial and cerebral ipsilateral lesions subsequently, since these tissues have a common cell progenitor. Given the small sizes of the ischemic foci, they might arise from the thrombosis of perivasculars. Although no responsible stenosis of the vessels was found, the slimmer left MCA could have played a role more or less. Since the stroke has been shown to be the cause of 10% - 15% of epilepsy [8], we speculated the ischemic foci to be remarkably associated with a substantially increased risk of developing epilepsy in our patient, and occurred in adulthood. In turn, this could also be one of the possible mechanisms underlying the epileptic presentation in LScs patients.

Due to the rarity of the cases, the evaluation of therapeutic benefit is limited. Currently much deficits exist in the treatment, and standard guideline is still absent. After the use of topical steroid and vitamin supplements, the lesion of our patient remained stable till maturity. Although steroid is one of the relatively accepted useful drugs for such lesions [3], it is still insensible to judge the stability solely owning to drug effect, or self-limited course of the lesion [2], or both. After admission, the patient was seizure free after levetiracetam treatment, but it is rather arbitrary to evaluate its effect now because of the refractoriness and intractability of the epilepsy caused by LSCS [2].

4. Conclusion

The patient was brought to our department due to seizures, and the initial reason was deduced to be associated with LScs. This case indicated that the cautiousness for the epileptic reason seeking is never excess, especially in adults. LScs complicated with epilepsy is not rare, but our case argued for the skepticism of the mechanism searching. Depending on the localized nature and nonprogressive course [9], LScs carries a relatively favorable prognosis, but affected central nervous system may limit the functional outcome.

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Informed Consent Form

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Conflict of Interest

None.

Contributions of the Writers

Haoyue Zhu contributed data collection and composition of this manuscript. Xiuli Shang contributed revision of this manuscript.

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Squamous Cell Carcinoma Arising from Aparaurethral Region

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Abstract

A 69-year-old man was referred to our hospital with dysuria and gross hematuria associated with a rapidly growing perineal mass. Serum squamous cell carcinoma (SCC) antigen level was high (2.4 ng/mL). Magnetic resonance imaging examination revealed a tumor posterior and inferior to the pendular urethra with a cystic lesion inside. Tumor resection together with total penectomy was performed. Pathohistological findings revealed well-differentiated SCC arising from the paraurethral region. The patient remained free of disease without adjuvant therapy at 70 months after surgery. To our knowledge, this is the second reported case of paraurethral SCC.

Keywords
Paraurethral, Squamous Cell Carcinoma, Perineal Mass

1. Introduction

Primary urethral carcinoma represents a rare malignancy accounting for <1% of genitourinary cancers. As for histological types, squamous cell carcinoma (SCC) is most common among both genders but adenocarcinomas are noted in 15% - 35% of cases among women [1]. As female urethral diverticula are considered to be associated with adenocarcinoma [2], paraurethral adenocarcinoma is relatively well reported [3]-[5]. Meanwhile, paraurethral SCC is extremely rare. We report a case of paraurethral SCC presenting as a rapidly growing perineal mass.

2. Case Report

A 69-year-old man with no past medical history was referred to our hospital complaining of dysuria and gross...
hematuria associated with a rapidly growing perineal mass. Physical examination revealed a stiff mass in the perineum. Digital rectal examination showed no abnormal findings. Serum laboratory data showed inflammatory findings, and among several tumor markers measured, only the SCC antigen level was slightly high at 2.4 ng/mL. Magnetic resonance imaging (MRI) examination revealed a tumor (45 × 52 × 55 mm) posterior and inferior to the pendular urethra with a cystic lesion inside, which was invading the corpus spongiosum (Figure 1). Urine cytology was positive, suggesting SCC. Cystourethroscopy revealed a constriction at the posterior urethra but no clear finding of urethral tumor. The patient then developed urinary retention and for which percutaneous cystostomy was performed. Percutaneous tumor needle biopsy showed SCC. Tumor resection and total penectomy were then performed. The bilateral testes were preserved. The excised tumor appeared as a solid and grayish mass, approximately 5 cm in size, with a yellowish granulomatous lesion next to the urethra (Figure 2). Pathohistological findings revealed well-differentiated SCC arising from the paraurethral region (Figure 3(A)). Neither the scrotal skin nor the urethra was directly infiltrated by the tumor (Figure 3(B), Figure 3(C)), while the urethral constriction was involved with the granulomatous lesion which was determined to be inflammation associated with tumor spillage (Figure 3(D)). The surgical margin was negative. Postoperatively, no additional treatment was administered. As of 70 months after surgery, the SCC antigen level was normal, and the patient remained free of disease.

![Figure 1. Magnetic resonance imaging revealed a tumor posterior and inferior to the pendular urethra. Large arrows indicate tumor and small arrows indicate the cystic lesion. Left panel: transverse plane. Right panel: sagittal plane.](image1)

![Figure 2. Macroscopic appearance of the tumor. The tumor is solid and grayish, apart from the urethra. Arrowheads indicate tumor and arrows indicate urethra.](image2)
3. Discussion

Although female paraurethral adenocarcinoma is relatively well reported [3]-[5], paraurethral SCC is extremely rare in both genders. To the best of our knowledge, only one case has been reported previously by Barua et al., who reported a 58-year-old man complaining chiefly of hematuria and a firm mass [6]. The tumor was located posterior and inferior to the bladder with a cyst inside. Histological findings revealed SCC arising within a paraurethral cyst. Their patient died 12 months after surgical removal of the tumor.

In the present case, a cystic lesion was identified within the tumor by MRI (Figure 1), but this lesion was collapsed at the time of the percutaneous biopsy by chance. Then the cyst was shrunk and compressed by the tumor in the resected specimen. There was a granulomatous inflammatory lesion next to the urethra with tumor cell spillage (Figure 3(D)). This suggests that tumor cells were spilling into the necrotic tissue due to inflammatory change, which resulted in the positive urine cytology. Neither the urethra nor the skin, which is a common primary site of SCC among perineal organs, was directly involved.

There are several hypotheses as to the origin of SCC, including ectopic squamous cells in the paraurethral tissue, the urethral glands such as Cowper’s gland or Skene’s glands, and a paraurethral cyst as reported previously [6]. Whereas the paraurethral cystic lesion identified on MRI is considered as a possible origin in the present case (Figure 1), the histological examination could not confirm this due to the shrinkage of the cyst by the previous biopsy.

Clinical signs of paraurethral carcinoma are assumed to be similar with urethral carcinoma [3]-[7]. Obstructive or irritative symptoms and hematuria are common modes of presentation of urethral carcinoma [1]. Urethral obstruction is evaluated by cystourethroscopy with cold cup biopsy but percutaneous needle biopsy may be required depending on the tumor location. MRI is a highly effective method to image the primary tumor to establish the loco-regional extent of disease at diagnosis. [1] In our case, the tumor invaded the corpus spongiosum without regional nodal involvement or distant metastasis. Since the surgical margin was negative, no additional treatment was added. Similar to urethral carcinoma, radiation therapy can be used as an adjuvant treatment if a surgical margin is positive [1]. No standard systemic therapy has been established due to the rarity of paraurethral carcinoma. In a retrospective study of 44 patients with advanced urethral carcinoma, cisplatin-based chemo-
therapy according to the primary histology was reported [8]. The median overall survival from chemotherapy initiation was 25.6 months. Although most urethral carcinomas respond well to cisplatin-based chemotherapy, further studies are needed to define the role of chemotherapy [1]. Since treatment modality other than surgery has not been reported for paraurethral SCC, complete resection should be tried to achieve long-term survival.

4. Conclusion

This report presented a case of paraurethral SCC in a 69-year-old man who achieved a long-term disease-free survival after surgery. Given a rarity of this disease, timely diagnosis and complete resection of tumor are critical for disease-free survival.

Informed Consents

Informed consent was obtained from the patient.

Conflict of Interest

None.

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Right Ventricular Myxoma—
A Case Report

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Abstract
From an epidemiologic perspective, cardiac myxomas are best divided into the following 2 categories: those that arise in isolation and those that arise in the setting of a syndrome (so called Carney Complex). The former account for about 90% - 95% of cases, while the later account for a minority of cases and those arise from the right or left ventricle constitute as 3% each. Real-time two-dimensional echocardiography has proved to be extremely useful in defining intracavitary masses. With two-dimensional echocardiography accurate visualization of the right ventricular body and outflow tract can be accomplished consistently. The acoustic nature and anterior location of the right ventricular myxomas make them appear as bright, mobile masses. The mobile nature of the tumor can easily be appreciated and its point of attachment, or stalk can be visualized accurately. Background of this case illustrates the transthoracic 2D echocardiographic pattern of right ventricular myxoma and its attachment by a pedicle to the anterior papillary muscle, masquerading as ball-valve thrombus and cardiac “stone” in tilted parasternal long axis-3 chamber views in a 15-year-old girl. Mahaim criteria to distinguish myxoma from organizing thrombus had been highlighted.

Keywords
Myxoma, Right Ventricle, Echocardiography, Ball-Valve Thrombus, Cardiac “Stone”

1. Introduction
Primary cardiac masses are rare and usually benign [1]. Approximately 75% of primary cardiac tumors are benign, and of those, myxoma is the commonest, constituting more than 50% of primary benign cardiac tumors. Those of ventricular origin are uncommon. The right ventricular myxomas are only found in 2% - 4% of cases [2].

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Although numerous theories have been posited regarding the etiology of cardiac myxomas, the precise histogenesis of these tumors remains to be determined. For a time, cardiac myxomas were believed to arise from mural thrombi [3]. However, the difference between myxomas and thrombi is substantial. Furthermore, histologically myxomas do not organize into fibrous tissue or show stratification, a classic feature of mural thrombi. Cardiac myxomas also behave differently from thrombi in tissue culture studies [4]. The body of evidence in support of the neoplastic nature of the myxomas has lead to the consensus that cardiac myxomas are not of thrombotic origin and are, indeed, neoplastic [5].

Studies have described the relationship between angiogenesis and tumor growth [6]. Cardiac myxomas produce vascular endothelial growth factor, probably inducing angiogenesis for tumor growth. Neoangiogenesis is involved in the development of masses in the heart, benign or malignant. The myxomas are vascular tumors and may be neovascularized by a branch of a coronary artery [7].

A cardiac myxoma is a neoplasm of uncertain histogenesis that occurs only on the endocardial surface. It has been postulated that the cells from which the tumors originate are the so-called reserve totipotential subendocardial cells capable of forming vascular structures [8] that have endothelial and neural markers. Studies with neuroendocrine markers using immunohistochemical techniques suggest that endocardial sensory nerve tissue is the origin of myxoma. The existence of an aneuploid cell population in a tumor is generally considered evidence that the lesion is neoplastic [9]. The presence of aneuploidy, as well as the findings of chromosomal abnormalities in the case of myxomas, suggests a neoplastic origin for this type of tumor.

Myxomas are polypoid, round, or oval, and typically pedunculated but can also arise in a sessile fashion. They are gelatinous with a smooth, papillary or lobulated surface and usually are white, yellowish, or brown. Histologic studies are characterized by the presence of lepidic cells (myxoma cells) embedded in a vascular myxoid stroma [10]. These cells are polygonal to stellate in shape with scant eosinophilic cytoplasm. Architecturally, myxoma cells form rings, cords, and nests that are often closely associated with capillaries and can also exist singly as stellate cells in a myxoid stroma.

Myxomas frequently have adherent thrombi on their surface. Myxoma cells exhibit immunoreactivity to calretinin (75% - 100%). Calretinin, in particular, has been proved quite useful in discriminating cardiac myxomas from mural thrombi and papillary fibroelastomas both of which lack immunoreactivity to this substance. Both the papillary excrescence and surface thrombi can be friable in nature and undergo embolization. One study suggests that the expression of the mucin gene MUC5AC within sporadic cardiac myxomas may correlate with a lower risk of embolization [11]. Grossly, two-thirds of myxomas are relatively compact and polypoid and unlikely to fragment spontaneously [12], while the other one-third are gelatinous and friable and, thus prone to fragment and embolize [13]. Secondary degenerative changes such as tumor necrosis were present in 8% of cases and calcification in 10% - 20%. Complete calcification of tumor may occur in rare cases [14]. Although the clinical course of cardiac myxoma is considered by most to be entirely benign, isolated cases of cardiac myxomas undergoing so-called malignant change have been reported [15] and documented the malignant potential of the myxomas with respect to local invasion of the vessel wall, recurrence, independent growth, distant metastasis and areas of hypercellularity. Reports typically cite areas of hypercellularity, necrosis, and atypia as a rationale for this designation. However, in many instances, a true malignant process and mitoses are typically absent. In addition, it is likely that many of these examples represent misdiagnosed myxoid sarcomas, a distinct and separate entity. To date, no study has been able to document consistent reproducible differences between sporadic and familial myxomas at the gross or microscopic level.

It is suggested that these neoplastic cells are of primitive multi-potential mesenchymal origin that persists as embryonic residues during septation of the heart and differentiate into endothelial cells, smooth muscle cells, angio blasts, cartilage cells, and myoblasts [16]. The cells of a cardiac myxoma are histologically and genetically different from the fusiform cells of soft tissue myxomas. Thus, myxomas are grouped under the category of benign tumors of pluripotent mesenchyme.

Mass forming reactive and pseudoneoplastic growths such as calcified amorphous tumor are often mistaken for calcified myxoma. Organization (proliferating fibroblasts, capillaries, and loose myxoid extracellular matrix) is conspicuously absent. Hemosiderin deposition and cholesterol clefts are rarely seen. Most cases show fresh thrombi on the surface—a potential source of emboli [17]. They are distinct from mural thrombi in that they lack significant fibroblast proliferation and organization and they can arise in any cardiac chamber.

An isolated right ventricular myxoma originating from anterior papillary muscle is uncommon and so this case had been reported.
2. Case Report

A 15-year-old asymptomatic girl was referred for screening echocardiography as a routine medical check-up. Her pulse rate was 80 bpm and blood pressure 110/80 mmHg. Physical examination revealed no abnormal findings and cardiac examination was clinically normal. Blood chemistry, X-ray chest and ECG were normal. Two-dimensional echocardiography revealed a 23.3 × 7.3 mm size myxoma originating from the anterior papillary muscle of the right ventricle with an attachment by a pedicle with the appearance of “cluster of grapes” as shown in Figures 1-4 and masquerading as ball-valve thrombus and cardiac “stone” as shown in Figure 5, Figure 6. Screening of family members revealed normal. She was advised periodic follow up.

3. Discussion

Cardiac tumors were first described in the 18th century by Boneti, however, many believe the description by Albers in 1835 is the first authentic report. Cardiac tumors, whether primary or metastatic are rare [18]. Myxomas are usually seen in adults. They are rarely seen in children, accounting for only 9% - 15% of all cardiac tumors from birth to adolescence. Right ventricular occurrences are rare and sporadic cases of right ventricular myxomas have been reported [19]. Czapek, in 1891, was among the first to provide a pathological description of a right ventricular myxoma [20]. 102 cases of myxomas originated from the right ventricle have been reported in...
Figure 3. Tilted apical 4 chamber view showing the myxoma visible on the anterior papillary muscle.

Figure 4. Tilted parasternal long axis-3 chamber view showing the myxoma masquerading as ball-valve thrombus with a bulbous end attached by a pedicle.

Figure 5. Tilted parasternal long axis-3 chamber view showing the myxoma masquerading as free-floating ball-valve, organized mural thrombus.
the literature up to 2002. The sites of origin in the right ventricle are tricuspid valve, pulmonary valve, anterior papillary muscle, free wall and RV (Right Ventricular) apex. Free wall attachment is more commonly seen than other locations. The mean age of patients with myxomas located in the right or left ventricle was 18.50 ± 6.36 years.

3.1. Echocardiography

The frequency of cardiac tumor is low with an estimated cumulative prevalence of approximately 0.15% by echocardiographic evaluation [21]. Echocardiography is an excellent way to make a diagnosis by noninvasive means [22] [23]. Right ventricular myxomas may manifest as single or multiple intracardiac homogeneous, polypoid or papillary masses attached to the endocardium by a pedicle (stalk) or with a broad base. In this patient, Figure 1 revealed a pedunculated, polypoid mass near the right ventricular apex, and attached by a pedicle to the papillary muscle as in Figure 2 with a appearance of “cluster of grapes” and visible on the anterior papillary muscle as in Figure 3.

In 1923, Hustein stated the myxoma as myxomatous “polyps”. They are thrombi in various stages of organization, which has little support now. It remains of prime importance, however, to consider the possibility of a mural thrombus masquerading as a pseudotumor whenever a polypoid tumor is observed attached to the endocardium. Criteria for distinguishing myxoma from organizing thrombi have been formulated by Mahaim [24] which was shown in the Table 1 given below.

Wood who first described the ball valve thrombus in year 1814 [25] and it is thought to be originating as a small mural thrombus. The thrombus gradually enlarges and form a projecting mass that remains attached by a pedicle. As the bulbous end of the thrombus enlarges, the pedicle lengthens and thin until eventually the thrombus separates or fragments. Thereafter as the thrombus spins freely, it acquires its characteristic smooth, polished appearance. In Figure 4, the myxoma mimicking as a ball-valve thrombus with a bulbous end attached by a pedicle.

Echocardiographic features of free-floating thrombus sometimes mimicked myxoma [26]. In myxomas, central areas of hyperlucency representing hemorrhage and necrosis, and the presence of calcification with echogenic foci can be detected by echocardiography. Following recurrent hemorrhage in the myxoma over time, impregnation of stromal connective tissue fibers with iron, calcium, and ceroid pigments may convert the myxoma into a sclerosiderotic nodule, termed as “Petrified cardiac myxoma” and masquerade as organized mural thrombi [27]. In Figure 5, the myxoma masquerade as free-floating ball valve, organized mural thrombus.

A calcified ball-valve thrombus sometimes mimic as a calcified myxoma. Calcification within a myxoma may follow tumor necrosis secondary to central infarction and repeated trauma and compression of the tumor once started, calcification may well encourage further necrosis by interfering with the blood supply of the myxoma and thereby cause the formation of a cardiac “stone” [28]. In Figure 6, the myxoma masquerade as a “cardiac stone”.
3.2. Future Perspective

The exact etiology of myxomas was unknown. Analysis of the causes of myxoma is important to formulate therapy to inhibit its growth. Earlier studies state that mutation in the gene Protein Kinase A (PKA) had been identified in patients with both syndromic and non-syndromic cardiac atypical myxomas [29] (atypical myxoma means that the myxomas are not localizing in left atrium and interatrial septum). A recent study states that no germline mutations were detected in myxomas [30]. Some studies also describe the role of neoangiogenesis in the development of myxomas [31]. A recently published article identified the nutrient coronary vessel to right ventricular myxoma [32] and it is understanding a relationship between angiogenesis and tumor growth. This knowledge is important for the possible creation of adjuvant therapies for inhibition of the tumor in future.

4. Conclusion

An isolated right ventricular myxoma originating from the anterior papillary muscle was visualized by transthoracic two-dimensional echocardiography in a 15-year-old female child and masquerading as ball-valve thrombus and cardiac “stone” in tilted parasternal long axis-3 chamber views of echocardiographic imaging is an interesting feature. It is a rare incidence detected in Thoothukudi Region of Tamil Nadu State in India.

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