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Case Report

# Pretibial Edema Is One of the Sign of Thyrotoxicosis A Case of Thyroid Heart Disease and Unilateral Pretibial Edema

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Thyroid heart disease is one of the many and frequent complication of thyrotoxicosis,[1] which also manifest in extra cardiovascular system.[2] Opthalmopathy is a well-known and well-studied complication of thyrotoxicosis, and another is dermopathy, which manifests as pretibial edema.

This case presentation describes a patient of long standing thyrotoxicosis with thyroid heart disease. In this particular case, the patient developed unilateral pretibial edema which posed a diagnostic challenge. In dealing with that, it would be important to consider several differential diagnosis. Some of the differential diagnosis of unilateral pretibial edema are actually not proven due to limited hospital stay, but an analysis of differential diagnosis will be presented and hopefully will lead to better recognition of clinical symptoms and signs of thyrotoxicosis, its complications and lead to appropriate diagnostic studies.

## Case illustration

Mr. AS, a driver, 46 years old came to our cardiac emergency unit due to palpitation. He complained of palpitation since 6 days before admission, the palpitation was not related to activities. Patients also experienced dyspnea, fever, and cough with white sputum. Dyspnea became severe in the last 2 days, especially during exertion, no episodes of paroxysmal nocturnal dyspnea or orthopnea. He also complained of lower leg swelling in the left side, since more or less 2 week before admission. No history of trauma. The swelling accompanied with mild pain by pressure, no blackened finger. The patient could still stand or walk. He said that he had never had leg swelling before.

The patient was a long standing patient of NCCHK since 1995 with a diagnosis of atrial fibrillation due to thyroid heart disease. The only drug that he consumed was digoxin 1 tablet per day. He visited Endocrinology clinic at Cipto Mangunkusumo General Hospital irregularly, and received treatment of PTU 300 mg/day. He quitted visiting Endocrinology clinic and his therapy since 2000, due to boring with medication, he also accused that the medication may cause kidney stone. He never visited any clinics nor consumed any medications lately, before he admitted to NCCHK. The patient denied of having hypertension, dislipidemia, diabetes mellitus, smoking and family history of heart disease.

On Physical examination: general appearance appeared moderately ill, composmentis, BP 108/74 mmHg, HR 110-120 bpm irregular, left and right radial pulse equal strength, RR 24x/min, body temperature 37$^{o}$C, Weight: 52,5 kg, Height: 162 cm, BMI

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20. Eyes: conjuctivae not anemic, sclera not icteric, normal eye sight, proptosis +/-, exopthalmos +/+. Jugular vein 5+2 cmH2O, mild diffuse thyroid enlargement, no bruit. Thorax: Lung – showed symmetrical breathing movement, sonor on percussion, and on palpation symmetrical normal fremitus, auscultation - vesicular, coarse rhonchi -/+ mid lung field, fine rales -/-. Heart – on inspection showed bulging chest, ictus cordis located at 2 cm lateral to midclavicle. On palpation; ictus cordis, located at 2 cm lateral to midclavicle, diameter 2 cm, no heaving or thrill. On auscultation the first and second heart sounds were normal, no murmurs, no gallop sound. Liver and spleen not palpable, normal peristaltic sound. Extremities were well perfused, the arterial pulse were normal. Pretibial nonpitting edema was detected in his left leg with minimal pain, no erythema or calor. There is hyperpigmentation, moist hand, and fine tremor/

*Electrocardiogram :* atrial fibrillation, QRS rate 108 bpm, QRS axis Right Axis Deviation, P wave and PR interval diffucult to interpret, QRS duration 0,08", rSR pattern in V1 (RBBB).

*Chest x-ray :* CTR 70%, normal aortic and pulmonary segment, cardiac waist was not seen, apex lateral upright. Lung field showed infiltrate and congestion.

*Laboratorium:* Hb 13,3 g/dl, Leuko 13900, Ht 38%, normal blood ureum and creatinin, His electrolyte level (Na, Cl and K) within normal limits. RBG 89, TSH 0,01, $T_3$ 2,44, $fT_4$ 2,11

*Transthoracic echocardiogram:* Showed dilated RV, RA, LA. No LVH, RV contractility reduced, LV contractility normal (EF 52%). Segmental analysis showed global normokinetic. The aortic valve consist of 3 cusps, with normal morphology and function. Trivial-mild mitral regurgitation, the leaflets were not prolapsing or calcified. Mild pulmonal and tricuspid regurgitation was detected with, TVG 27 mmHg. E/A > 2, DT 100 msec, AoVmax 1,2 m/s, mPAP 25 mmHg

*Femoral Duplex sonography :* Normal flow in arteries and veins of both legs. Deep vein thrombosis are not detected in both legs

The patients was diagnosed as thyrotoxicosis, thyroid heart disease, AF rapid response, Bronchopneumonia and Pretibial myxedema, And treated with propranolol 5 mg/8hrs, PTU 100 mg/8hrs, Digoxin 0,25 mg/day, Furosemide 40 mg/day, Cefotaxime 1 gr/8hrs IV, anticoagulant Simarc-2 was given based on trombotest/INR. He was discharged on 4th day of hospitalization, no palpitation, no dyspnea, pretibial edema still present, no pain, heart rhythme AF normoresponse. The patient was asked to resume consultation to endocrinologist with a remark about his pretibial edema. The patient was also scheduled to visit outpatient clinic at NCCHK within 1 week.

## Discussion

The diagnosis of thyrotoxicosis and thyroid heart disease in this patient have been established with the diagnosis of thyroid heart disease and atrial fibrilation since 1995. The patient also visited Endocrinology Clinic at Cipto Mangunkusumo Hospital for treatment of thyrotoxicosis due to Graves Disease, but stopped in 2000.

The remaining pathology, unilateral pretibial edema, poses a diagnostic problem that need to be explored. Localized myxedema, or thyroid dermopathy, is an infrequent manifestation of autoimmune thyroiditis and, in particular, of Graves' disease. About 0.5–4.3% of patients with a history of thyrotoxicosis have thyroid dermopathy, and 15% of patients with severe Graves' ophthalmopathy have this cutaneous manifestation,[3] although other reports as high as 30%.[4] It is characterized by localized thickening of the skin, forming a localized nonpitting edema.[5] Commonly localized in the pretibial area, it is therefore often referred to as pretibial myxedema (PTM). Nonpitting edema was the most prevalent form of dermopathy (43.3%), and the pretibial area was the region most commonly involved (99.4%). Unilateral lesion was found quite frequently (44.5%). The majority of patients with dermopathy had ophthalmopathy (97.0%).[3]

Diagnosis of PTM was made in patients by the presence of the typical clinical picture. The presentation included raised lesions of the skin, usually in the pretibial area. Hyperpigmentation and hyperkeratosis were present in some cases, as was hyperhidrosis. The lesions were occasionally indurated and the hair follicles prominent so that the lesions had an orange peel (peau d'orange) or pig skin appearance and texture. Dermopathy was classified into one of the following four forms: nonpitting edema accompanied by typical skin color changes, plaque, nodular, or elephantiasic. The area of skin involvement was pretibial in 166 (93.3%), pretibial and feet in 7 (3.9%), pretibial and upper extremities in 2 (1.1%). The clinical form of PTM was nonpitting edema in 77 (43.3%), plaque in 48 (27.0%), nodular in 33 (18.5%), elephantiasic in

5 (2.8%), and unclassifiable and/or unknown in 15 (8.4%). The hallmark finding on biopsy specimens from these skin lesions is increased levels hyaluronic acid concentrations, often 6 to 16 times higher in these lesions than in normal skin. Skin biopsy specimen from patient with localized myxedema showing separation and fraying of connective tissue fibers and edema.[3]

Generally, PTM is only of cosmetic concern, but 12% patients experience pain or discomfort. The treatment of dermopathy is usually symptomatic. Antithyroid is effective in controlling systemic thyroxin response, but has little effect once dermopathy has developed. Nevertheless, antithyroid therapy is beneficial to reduce the rate of progression of dermopathy. Given the relatively benign nature of this problem, topical corticosteroids are more likely to be used than systemic therapy. A trial of 4–6 wk may be reasonable, while attempts at achieving long-term remission were unsuccessful because of undesirable side effects. With this therapy, 24% patients had partial remission and 26% complete remission.[3]

It is important for cardiovascular physician to consider several disease pathologies that may result in unilateral pretibial edema, some are related to peripheral vascular disease.

Causes of swelling of lower limb in this patient can be descibed in the following list:[6,7]

- Deep vein thrombosis
- Cellulitis
- Joint effusion or haemarthrosis
- Haematoma
- Baker's cyst
- Torn gastrocnemius muscle
- Haemangioma
- Chronic venous insufficiency
- Venous obstruction
- Lymphedema
- Tumor
- Trauma
- Pretibial myxedema

Other (mostly bilateral): heart failure, hypoproteinaemia, such as cirrhosis, nephrotic syndrome.

Among the above mentioned possibilities, some could be excluded on the basis of history and physical findings. These include trauma, joint pathologies (effusion, hemarthrosis, Baker's cyst), tumor, torn gastrocnemius muscle and hemangioma. Systemic disease such as heart failure, cirrhosis and nephrotic syndrome is very unlikely as a cause of unilateral limb edema. The edema associated with heart failure is bilateral, dependent, and pitting.[8,9] Unilateral or nonpitting edema is not related specifically to heart failure, and other causes such as vascular insuficiency, myxedema, or lymphedema should be suspected.[9]

Deep venous thrombosis (DVT) of the iliac, femoral, or popliteal veins is suggested by unilateral leg swelling, warmth, and erythema. Tenderness may be present along the course of the involved veins. There may be increased tissue turgor, distention of superficial veins, and the appearance of prominent venous collaterals. The most common complaint is calf pain. Examination may reveal posterior calf tenderness, warmth, increased tissue turgor or modest swelling. Increased resistance or pain during dorsiflexion of the foot (Homans' sign) is an unreliable diagnostic sign.[10] The noninvasive test used most often to diagnose deep venous thrombosis is duplex venous ultrasonography (B-mode, i.e., two-dimensional, imaging, and pulsewave Doppler). By imaging the deep veins, thrombus can be detected either by direct visualization or by inference when the vein does not collapse on compressive maneuvers.[11] The positive predictive value of duplex venous ultrasonography approaches 95% for proximal deep vein thrombosis. In the calf, because calf veins are more difficult to visualize than proximal veins, the sensitivity of this technique is only 60 to 75%, although its specificity is 95%.[10]

Should we consider DVT as the cause of unilateral pretibial edema in this patient? The answer is absolutely yes. In patients with thyrotoxicosis, thromboembolic event is not rare. The most commonly reported thromboembolic events are emboli related to atrial fibrillation. In addition to that, the thrombotic predisposition may not only result from the arrhythmias but may also be augmented by a prothrombotic status stimulated by high levels of thyroid hormone. Deep vein thrombosis had also the most severe consequences compared with other differential diagnosis, therefore its presence should be sought immediately. In this particular case, DVT seems unlikely as the cause of pretibial edema based on the findings in duplex sonography.

Cellulitis is an acute inflammatory condition of the skin that is characterized by localized pain, erythema, non pitting edema, and heat. Cellulitis may be caused by indigenous flora colonizing the skin and appendages (e.g., *S. aureus* and *S. pyogenes*) or by a wide variety of exogenous bacteria. Usually there would be an obvious portal of entry.[12] This patient had contracted bronchopneumonia but there was no clear sign

of skin damage that may predispose to cellulitis. From a search of extensive literature, the far-flung spread of lung infection to soft tissue in pretibial skin is extremely rare.[13]

Lymphedema is also one possibility that had not been explored. Lymphedema is generally a painless condition, but patients may experience a chronic dull, heavy sensation in the leg, and most often they are concerned about the appearance of the leg. Lymphedema of the lower extremity, initially involving the foot, gradually progresses up the leg so that the entire limb becomes edematous. In the early stages, the edema is soft and pits easily with pressure. In the chronic stages, the limb has a woody texture, and the tissues become indurated and fibrotic. At this point the edema may no longer be pitting. The evaluation of patients with lymphedema should include diagnostic studies to clarify the cause. CT scan appear to be efficacious. Lymphoscintigraphy and lymphangiography are rarely indicated, but either can be used to confirm the diagnosis or to differentiate primary from secondary lymphedema.[14] In this patient, repeated leg infection or groin tumor is absent in the history and physical examination. Furthermore, edema in lymph obstruction is invariably pitting at an early stage. Nevertheless, the diagnosis of lymphedema could not be completely rejected since there was still some diagnostic test to be performed, notably CT or lymphoscintigraphy.

Pretibial myxedema, a complication of thyrotoxicosis, should be considered in this case. Many of the known manifestation of thyroid dermopathy is present in this case, such as nonpitting nature of edema, localized in pretibial area, hyperpigmentation, mild pain – painless, existence of other thyrotoxicosis manifestation (opthalmopathy), and unresponsiveness to short treatment of diuretics. The only proven diagnostic tools that is lacking is skin biopsy.

## Conclusion

- Deep venous thrombosis should always be a major suspicion in this patient since he has: 1) thyroid heart disease with atrial fibrillation, 2) thyrotoxicosis with increase prothrombotic state. Venography may be indicated if duplex sonography is doubtful.
- Cellulitis should also be suspected even in the absence of frank skin damage. The lack of local sign of infection especially erythema and the duration of 2 weeks reduce the possibility of cellulitis as a cause of edema. The link between bronchopneumonia and cellulitis is also weak.
- Lymphedema should be considered and explored. The likelihood of lymphedema as a cause of leg edema in this patient is remote since the presence of nonpitting edema and mild pain on pressure (usually painless or pain at late presentation). The diagnosis of lymphedema should be based on documented lymph stasis preferably by lymphatic vessel studies.
- The proposed diagnosis of pretibial myxedema was based on clinical presentation, preferably augmented by skin biopsy and exclusion of other differential diagnosis.

Summary of differential diagnosis of unilateral pretibial edema in this patient:

Summary of differential diagnosis of unilateral pretibial edema in this patient:

| | Pretibial myxedema | Deep Vein Thrombosis | Cellulitis | Lymphedema |
|---|---|---|---|---|
| History | Thyrotoxicosis, opthalmopathy | DVT risk factors present | Skin abrasion, trauma | Tumor, filariasis |
| Edema | Non pitting | Pitting | Non pitting | Pitting (early), nonpitting (late) |
| Pain | +/- | ++ | ++ | - |
| Inflammation | - | + | ++ | - |
| Superficial vein enlargement | - | ++ | - | - |
| Diagnostic studies | Skin biopsy | Duplex sonography, Venography | Culture | CT, Lympho Scintigraphy |

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