Touraine-Solente-Gole Syndrome with blepharoptosis

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Abstract

Touraine-Solente-Gole syndrome, pachydermoperiostosis, is a primary, inherited or idiopathic hypertrophic osteoarthropathy, which affects the bones, skin and supporting tissue and is clinically manifested by a symptomatic triad: pachyderma (thickening of the skin), periostosis, (excessive, exuberant, symmetrical neoformation of subperiosteal bone tissue in the long bones) “clubbing” fingers and other minor criteria including blepharoptosis with pachyderma. We present two clinical cases with Touraine-Solente-Gole syndrome in which there is the symmetrical bilateral blepharoptosis, with hypertrophic skin and narrowing of the eyelid slit vertically: the first case presented the complete form, while the second form is partial. The management of these clinical cases consisted of the recommendation of symptomatic medical treatment and surgical treatment with excision of excess hypertrophic skin, partial resection of the muscle that lifts the eyelid, anchoring the remaining lifting muscle to the frontal muscle by two non-absorbable threads introduced by tunneling; an effective personal method in the cases presented. We suggest medical treatment of blepharoptosis with injection into the subcutaneous eyelid tissue of VEGF inhibitors repeated every 30 days.

Keywords: Pachyderma, Periostosis, “Clubbing” Fingers, Pachydermoperiostosis, Blepharoptosis

INTRODUCTION

Touraine-Solente-Gole syndrome or pachydermoperiostosis is a clinical variant of primary, inherited or idiopathic hypertrophic osteoarthropathy; it is a rare genetic syndrome (0-16%), which affects the bones, skin and soft tissues [1].

Hypertrophic osteoarthropathy is a systemic disease that can lead to complications through excessive growth of supporting tissue and bone tissue, or can be associated with multiple serious diseases, some malignant [2].

Hypertrophic osteoarthropathy is:
- primary - pachydermoperiostosis or Touraine-Solente-Gole syndrome, hereditary or idiopathic, which represents 3% of all osteoarthropathies and which is associated with damage of the skin, bone and supporting tissue.
- secondary - associated with severe diseases: bronchiectasis, cystic fibrosis, congenital heart disease and biliary cirrhosis, inflammatory bowel disease, paraneoplastic syndrome (Table 1).

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Clinical signs | Primary | Secondary
--- | --- | ---
age | early onset | late onset
progression | slow progression | rapid progression
cutaneous manifestations | predominate | rarely
joint pain | minimal | severe
involvement of the epiphysis | present | absent
other associated diseases | no | bronchiectasis bronchogenic carcinoma, lung abscess

**TABLE 1: Differential diagnosis of primary / secondary hypertrophic osteoarthropathy (3)**

Touraine-Solente-Gole syndrome is more common in men (M/F - 7/1) in whom it has a more severe evolution and manifests itself clinically in childhood or adolescence at puberty and after 5-20 years of progression it stabilizes [3].

Clinically, the disease is characterized by major and minor criteria for a positive diagnosis [4]:

**Major Criteria:**

- **Pachyderma** – thicken and wrinkled skin with dermal and glandular hypertrophy which accentuates the features of the face and scalp, scalp with cerebriform appearance, with accentuated and deep wrinkles, facial anomalies with coarse facies, sometimes leonine, with deep nasolabial folds.

- **Periostosis** – excessive, exuberant, symmetrical neoformation of subperiosteal bone tissue at level of long bones, arms, legs, metacarpus, metatarsus, phalanges, with irregular periosteal proliferation, predominantly distal.

- Bone scan shows active inflammation with increased osteoblastic activity

- the first affected is the diaphysis, the involvement of the metaphysis and the epiphysis indicates progression of the disease

- associated joint abnormalities: arthritis, thickening of the periarticular tissue, acrosteolysis, myelofibrosis, periosteal ossification

- in children, the clinical appearance may be rheumatoid arthritis with “clubbing” fingers and joint pain with periostitis that tends to involve the pineal gland bringing about the alteration of long bones.

- **“clubbing” fingers** - hippocratic fingers - with the widening of the terminal part of the fingers (hands, feet), with the decrease of the normal angle between the nail and the nail bed “clubbing” fingers occur by increasing capillary density, edema, hyperplasia of fibroblasts and smooth muscle of the vessels by the intervention of the VEGF that produces abnormalities of vascularization, hypoxia and chronic inflammation with perivascular lymphocytic inflammation [5,6].

Touraine-Solente-Gole syndrome, pachydermoperiostosis is characterized by abnormal proliferation of skin, bone tissue and soft tissue (8), by different combinations between dermatological changes, bone, rheumatological manifestations and “clubbing” fingers (5).

**Minor criteria**

- excessive sweating with sebaceous gland hypertrophy

- arthralgias, joint effusion

- gastrointestinal disorders: peptic ulcer, chronic gastritis, Crohn’s disease

- at vascular level: peripheral vascular stasis, congenital heart disease

- eyes – thickened eyelids accompanied by blepharoptosis, acne, hyperhidrosis
– eyelid ptosis is not very common and occurs through a mechanical process, generated by skin hypertrophy or glandular associated with eyelid dysfunction [7].

The positive diagnosis of Touraine-Solente-Gole syndrome is made by the presence of two of four criteria; family history, “clubbing” fingers, pachyderma, bone changes with radiological changes.

Touraine-Solente-Gole syndrome has three clinical forms [3,7]:
- complete 40%: pachyderma, periostosis, “clubbing” fingers
- incomplete 54%: without pachyderma
- mild 6%: pachyderma associated with small bone changes, with minimal, limited periostosis, is predominant.

Touraine-Solente-Gole syndrome is an evolutionary condition which generally stabilizes after 5-20 years of progressive evolution, followed by orthopedic disabilities and neurological sequelae and has varied and multiple clinical manifestations in a random association.

Touraine-Solente-Gole syndrome is AD, with incomplete penetration and variable expression, rarely AR, very rarely X linked.

The pathogenesis of Touraine-Solente-Gole syndrome is unclear, but multiple factors are involved [8]:
- increased PGE2 prostaglandin level accentuates the activity of osteoblasts, osteoclasts, with acrosteolysis and new subperiosteal bone formation.
- PGE2 elevation is associated with mutation in the HPGD gene located on chromosome 4q33 - q34.
- patients with homozygous mutations have elevated PGE2 levels.
- the role of endothelial vascular growth factor VGF, which causes angiogenesis with the growth of neovessels, differentiation of osteoblasts that may explain the excess fibroblastic formation and “clubbing” fingers.

The positive diagnosis is established by correlating the clinical data with the laboratory examination and the radiological examination that highlights typical bone changes with periostosis, acrosteolysis [9-11].

Presentation of clinical cases with Touraine-Solente-Gole Syndrome

Clinical Case 1.

Patient, F.V, 63 years old, diagnosed with Touraine-Solente-Gole syndrome, with no family history of osteoarthropathy, but with a personal history of evolutionary disease with onset 10 years ago. The patient addresses the ophthalmology service for bilateral, symmetrical blepharoptosis, with progressive evolution, with thickened skin in eyelids especially the upper ones with reduction of the eyelid slit in the vertical plane – both eyes-4mm (Figure 1a and b).
Figure 1a and b: The appearance of the face. The skin of the forehead is thickened and wrinkled, the eyelids are thickened.

Ophthalmological examination: - visual acuity in both eyes 1/6 ccp, eye pressure = 15mm Hg, visual field:
- peripheral narrowing in the upper half due to the position of the eyelids
- thickened eyelids, blepharoptosis
- normal anterior pole
- eye fundus in both eyes, severe myopia, myopic choroidosis

Upon the general examination, the patient presented with morphological aspects, characteristic for pachydermoperiostosis:
- Pachyderma - thickened skin on palms, soles, wrinkled thickened forehead, scalp with hypertrophic, wrinkled skin, cutis verticis gyrata, accentuated facial features, coarse face with thickened skin, deep nasolabial fold
- severe bilateral blepharoptosis with thickened skin, more pronounced on the upper eyelid with the reduction of the eyelid fissure, with reduced function of the muscle that lifts the upper eyelid (Figure 2.a, b and c).

Figure 2.a, b and c- Scalp skin furrowing

- “clubbing” fingers with sausage appearance (Figure 3a and b)
Figure 3a and b: “Clubbing” fingers, skin hypertrophy.

- minimal bone abnormalities, with abnormal enlargement of the hand, knee, foot
- normal X-ray of the skull, including the Turkish saddle
- radiograph of long bones, lower limbs show minimal subperiosteal reaction, without narrowing of the medullary cavity.

Laboratory examination: normal hemoleukogram, ESR, PCR, creatinine, bilirubin, transaminases, alkaline phosphatase, ionogram, rheumatoid factor, ANA; growth hormone analysis, parahormone, thyroid profile, venereal disease - no changes.

- biomarkers: PGE$_2$ urinar, IL$_6$

ENT examination - bilateral subacute maxillary sinusitis, right retromandibular lymphadenopathy.

EKG examination - sinus rhythm, AV 75b / min, discrete terminal phase changes.

Ultrasound, CT scan, abdomen - no changes.

Skin biopsy - adenomatous proliferation of the cutaneous epithelium and Meibomius glands, with cystic dilatations, dermal edema with mucin deposits, dermal fibrosis with degeneration of elastic Fibers.

By correlating the data obtained by clinical examination, laboratory, radiological, internal medicine exploration, endocrinology, ENT, Orthopedics, the diagnosis of Touraine-Solente-Gole syndrome, the complete form, was established.

Clinical Case no. 2
A 34-year-old patient, B.T., presents 4 years before hospitalization, at the level of the upper eyelid in both eyes, alump similar to a chalazion, which extended in the following years and included the entire upper eyelid at the level of both eyes, diagnosed in the outpatient clinic with chalazion after 4 years of evolution. The patient underwent outpatient surgery for both eyes, 4 years ago. The patient was sent for hospitalization 4 years after surgery of chalazion, with the diagnosis of chalazion, bilateral blepharoptosis.

The general clinical examination performed in the hospital directs the diagnosis to Touraine-Solente-Gole syndrome, partial form, by highlighting:

- Pachyderma with forehead with thickened and wrinkled skin, skin thickening on the hands and feet
“clubbing” fingers
- Minimal bine manifestations
- Minimum criteria present for positive diagnosis with: palmoplantar hyperhidrosis,
- Joint pain, aspiration of synovial fluid, non-inflammatory, non-hemorrhagic, aseptic, hypertrophic gastritis

Ophthalmological examination - thickened eyelids, with cutaneous hypertrophy, more accentuated in the upper eye lid with narrowing of the eyelid slit in both eyes-6mm, with blepharoptosis
- Normal anterior pole, normal eye fundus
- Visual acuity in both eyes - 2/3; eye pressure 15mm Hg, visual field - upper half amputation.

The confirmed clinical diagnosis of this case is of Touraine-Solente-Gole syndrome, incomplete form, with blepharoptosis. These two cases have clinical manifestations of Touraine-Solente-Gole syndrome, in which the symptomatic associations are multiple and varied, the cases presented being dominated by sequelae ocular pathology - bilateral blepharoptosis that affects the clarity of visual function, but also facial aesthetics.

Touraine-Solente-Gole syndrome is a self-limited condition, with progressive evolution, followed by sequelae, confirmed by severe bilateral blepharoptosis in the presented cases (7,8).

The dominant clinical element of the syndrome, in the presented cases, was the palpebral pachyderma with blepharoptosis which represented the initial primary element of positive clinical diagnosis in case 2. Progressive bilateral palpebral ptosis, with evolution and aggravation in 8-10 years in the first case, 4 years in case 2, was the main element of positive diagnosis in case 2.

The management of Touraine-Solente-Gole syndrome is medical and/or surgical, depending on the clinical manifestations of the disease.

**Symptomatic Medical Treatment**
- Anti-inflammatory: - NSAIDs in which selective COX2 is preferred, which inhibits cyclooxygenates
- Etoricoxibum - 60mg p.o.
- Corticosteroids - Prednisolone - 5mg p.o. in association with NSAIDs decrease the formation of inflammation mediators, with reduction of inflammation and pain undercorticosteroid treatment (induce gastropathy)
- Infliximab - monoclonal antibody that blocks the biological action of TNF α (tumour necrosis factor α) which promotes increased bone resorption
- reduction of the process of bone neoformation - Bisphosphonates – oral Pamidronate or Risedronate 35mg/week reduce bone remodelling and soothes pain; Zoledronic acid 5mg.IV
- Tamoxifen may be needed for the treatment of bone and joint pain
- Decrease in skin manifestations - Retinoids - Isoretinoid 20mg., oral and ointment, induceapoptosis of the sebaceous glands, decrease RNA procollagen in fibroblasts
- Colchicine inhibits cell division and the inflammatory process, inhibits the chemotactic activity of leukocytes with the reduction of pachyderma
- Botulinum toxin type A, for facies

Surgical Treatment
For face / scalp pachyderma, plastic surgery for cosmetic purposes:
- Removing excess skin
- Wrinkle resection
- Surgical treatment of ptosis
- Skin excision of the excessive eyelid
- Resection of the lifter muscle, aponeurotic resection with advanced suture above the tarsus muscle
- Blepharoplasty with horizontal tarsal resection and skin excision

Particularity of the cases - the major clinical manifestation in both cases and the reason for the presentation of the patient in the hospital service was symmetrical bilateral blepharoptosis with progressive evolution, with palpebral changes, with skin hypertrophy

In case 2, the palpebral changes oriented the positive diagnosis towards the diagnosis of Touraine-Solente-Gole syndrome, a diagnosis confirmed by the systematic clinical examination.

The cases presented required:
- symptomatic medical treatment indicated in this pathology: NSAIDs, corticosteroids, retinoids, bisphosphonates
- surgical treatment of blepharoptosis was performed unilaterally in the first case and bilaterally in the second case - removal of excess hypertrophic skin
- resection of the muscle lifting the upper eyelid
- anchoring the remaining lifting muscle to the frontal muscle by two
- non-absorbable threads introduced by tunneling (personal method)
- postoperatively, the opening of the eyelid slit was widened, so we considered effective the surgical treatment.

CONCLUSIONS
The cases presented with the diagnosis of Touraine-Solente-Gole syndrome are personalized by the presence of clinical manifestations dominated by blepharoptosis, but with the presence of signs of Touraine Solente-Gole syndrome - complete and mild form.

The personal method of surgical treatment, with the resection of the lifting muscle and its anchoring to the frontal muscle was effective by widening the opening of the eyelid slit postoperatively.
We believe that medical treatment could benefit from local treatment with VEGF inhibitors, by local injection of antiVEGF, repeated as needed.

REFERENCES


