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Gardner-Diamond's Syndrome: Literature review

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ABSTRACT

Gardner Diamond's Syndrome is a rare autoimmune vasculopathy of little known etiology. It consists of outbreaks of painful atraumatic ecchymotic lesions in any part of the body, particularly in the lower limbs and thorax of young women, associated to the appearance of psychiatric imbalance or disorders, suggesting emotional distress as the main trigger and perpetuator of such lesions.

Keywords: Gardner Diamond, Autoimmune Vasculopathy, Emotional Stress

Introduction

Gardner Diamond Syndrome (*Autoerythrocyte sensitization syndrome, Psychogenic purpura*)[1] is a rare autoimmune vasculopathy[2] of little known etiology. In a psychiatric or subjacent psychosomatic disorder context, it is a clinical profile characterized by atraumatic painful ecchymotic lesions.[3-4]

It follows a path of relatively benign, variable severity, with relapse-remission behavior, and recurrence of lesions even after 38 years from the start of the disease[5-6]

Descriptions from the early XX century are found in literature:

Schindler, 1927, described 16 patients with similar skin hemorrhages, stating such lesions disappeared after several sessions of hypnosis.

Jacobi, 1929, described two cases of patients with purpura and psychiatric associated disorders. Nevertheless, the first official reports are from 1955 when Gardner and Diamond described the entity in four women[5]. Later, Ratnoff and Agle named it *Psychogenic purpura* due to the association with psychiatric disorders[7]

Current literature on this matter is based on cases reported (162 up to 2009, of which

only ten involve men) [2-8-9-10] In 1971 Lababidi & Friedman, described the first case of Psychogenic purpura in a man; after that, cases describe on the male sex are but a few, most of them take place during the third decade of life with lesions similar to those found on women. It is assumed that men make up 5% of the frequency of the disease [11-12-13] Ratnoff reported the largest series of cases in 1989. This author describes 71 patients, most of them females, with lesions compatible with such entity; the ecchymoses appear weeks or days after trauma or surgery, but the most frequently related factor was emotional stress. The response to the skin test (see below) was erratic, only 59% of all patients had a positive response. Among the non-skin manifestations, patients presented cephalea, paraesthesia, syncope and diplopia (in some cases monocular). The prevailing psychiatric disorders were depression, sexual difficulties, and obsessive-compulsive disorders. [14]

EPIDEMIOLOGY

As mentioned before, it is a rare entity from which we have little accurate statistic data. Hitherto an entity prevailing in women, approaching their thirties (and varying between 19-72 years of age), however cases on men and children have also been reported[6]

ETIOLOGY

Little has been stated about the etiology of the entity. Multiple factors related to appearances of lesions have been suggested, including immunologic, hematologic, hormonal, vascular and subjacent inflammatory conditions [15-16]; also, associations between the neuroendocrine axis and behavior have been studied seeking to explain the way in which psychiatric disorders have somatic manifestations. [17]

Immunological/inflammatory: In principle we are dealing with an autoimmune vasculopathy, of which phosphatidylserine, an erythrocyte membrane phospholipide[1], appears as its primary antigen. Also suggested were blood cell or vascular endothelial stroma - or structure – distortion, and oxidative distress-induced damage, causing a phenomenon of local inflammation in predisposed subjects. Strunecka, using indirect immune fluorescence (IIF), showed that over 50% of the phosphatidylserine present on GDS patients´ RBCs is redistributed over the outer cell membrane layer[5,18-19-20-21] Similar inflammatory phenomena have been recounted after exposure to other substances such as Serum, platelets, proteic

derivates, histamine, histidine, serotonin, tryptophan, trypsin, DNA and copper[6-22-23]
It has been related to immunologic phenomena, taking into account reported cases in patients with autoimmune diseases like SLE, immune complex nephritis, idiopathic thrombocytopenic purpura; as well as those with low complement levels[24] and positive anticardiolipin antibodies[1]; establishing scenarios in which there may be deterioration of symptoms following emotional distress and where use of oral steroids might be useful for treatment.

Vascular: Merlen suggested regulation alteration in venous capillary tonus by fluctuations in the kinin-kallikrein system; related to fibrin endothelial synthesis alteration.[5-25]

Hematological: this work has been postulated to account for reports of platelet dysfunction, thrombocytosis, entity related platelet III factor deficiency [6-26]; although hemostasia assessing paraclinicals appear normal in these patients, there seems to exist a defect in the primary hemostasia, considering that 2/3 of the patients present menorrhagia, epistaxis, gingivorrhagia and gastro-intestinal bleeding [3-4] some authors suggest an increase in plasmatic fibrinolytic activity along with secondary bleeding[27]

The etiological component of emotional stress on the genesis of lesions is not clear, however the neuroimmune system is deemed as mediator on the appearance of lesions. [28-29]

CLINICAL

The disease development it's usually preceded by a series of mechanical wounds (surgery or trauma) [30] by which blood extravasation and exposure to antigens. It is clear though, that emotional stress acts as main trigger and perpetuator of the lesions [3]. Also, cases were symptoms are worsened by exposure to copper have been reported: a 19 year old patient presented symptoms improvement when her IUD (Intrauterine Dispositive) was removed and reappearance of the lesions with IUD reimplantation [31]Skin symptoms are preceded by prodromes, general discomfort and fatigue. [2] Afterwards, lesions may appear in any part of the body (mainly on lower limbs and thorax and may even involve some areas of the face) [1]

There is pain and pruritus in the skin area where lesions will appear; a skin induration may be observed after 4-5 hours, and in 24-48 hours it turns into a painful ecchymotic patch, 3-10 cm in diameter and lasting 1 or 2 days. After this time, the lesion starts discoloring until it turns yellowish before finally disappearing

leaving no scars whatsoever in a matter of in 1 to 2 weeks. [2-5-32] As described in **Table 1**, over 50% of all patients present non-skin related symptoms [5-30-33-9-17-34]. Manifestations are usually benign and carry a good prognosis; however the Gardner-Diamond Syndrome has been identified as the source of membranous glomerulopathy. [35]

Associations with other pathologies as Glomerulonephritis, lymphoid interstitial pneumonia, angioimmunoblastic lymphadenopathy as well with two patients with Cerebrovascular disease (PVD)[5] and compartment syndrome has been reported. Most frequent psychiatric disorders are depression, anxiety, emotional lability, guilt feelings, sexual issues, masochism, hysteric and borderline personality, and obsessive-compulsive behavior.

HISTOPATHOLOGY

Histological studies on the ecchymotic lesions reveal skin edema, erythrocytes extravasation and perivascular acute inflammatory infiltration. some iron compatible pigmentation pools on macrophages, have also been observed. Atypical Leukocytoclastic changes may show on infiltration or fibrinoid degeneration of vessels. Diagnosis in most cases does not require hystopathological assessment.[1-5]

LABORATORY TESTS

There are no GDS-lab specifics. Hematological parameters, including hemoglobin, hematocrit, platelets count, peripheral extension, globular sedimentation rate, electrolytes, bleeding time, prothrombin, thrombin, partial thromboplastin timing, and clotting factors, are usually within normal limits[2], nevertheless there are reports of patients with typical lesions and thrombocytosis[36]

DIAGNOSIS

It is mainly clinic, where previous episodes of physical or emotional stress, combine with typical skin lesions, usually in women with regular coagulation parameters. With infiltration patches and plates, followed by inflammation and by areas of painful ecchymosis within the following 24 hours [37]

Skin test:

Intradermic injection of 1ml of 80% washed erythrocytes suspension originated on the patient herself. This test is positive if GDS typical inflammatory lesions appear within 24 hours (there are reports of appearance of lesions 96 hours after injection)[38], and then, gradually, a progression to ecchymosis takes place [2]. The test is made in non-accessible hands

skin areas to prevent factitious lesions. A negative test does not exclude diagnosis[10.]

DIFFERENTIAL DIAGNOSIS

Differential diagnostics include, among other coagulopathies [39,] conditions related to bleeding such as idiopathic thrombocytopenic purpura; Henoch-Schoenlein purpura, Ehlers-Danlos Syndrome, contact Dermatitis, systemic erythematous lupus (SEL), Munchausen disease, compartment syndrome and Weber-Christian panniculitis[2] Due to its low incidence in children, it is important to dismiss physical abusing as well as other pediatric psycho-cutaneous disorders (trichotillomania, psychogenic excoriation, acne, dermatophagia, etc.)[10] It is important to tell it apart from other coagulation disorders such as acquired VIII factor inhibitor, hemophilic pseudo-tumor and skin necrosis related to cumarinics.[40]

TREATMENT

The treatment of GDS is so difficult that this entity is also known as *dermatosis sine therapia.* There are neither sufficiently effective methods nor randomized studies to use as a reference point for choosing the best therapy. Steroids, antibiotics, analgesics, antihistaminics, glucocorticoids and cytostatics[5-6-41] have been used, some patients presented remission with high doses of immunoglobulin[42] with no clear benefit in any of them. Considering the underlying psychological context [1] all cases reported insist upon the relevance of psychotherapy. Hypnosis and psychotherapy were effective at improving skin lesions in young patients [10- 43-44-45] Using medications to regulate vascular tonus has been suggested [5]; however betablockers [46-47-48], bioflavonoids and calcium channel blockers, have not shown meaningful therapeutic effects [49-50]

Conflict of Interest: None declared.

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Table 1. Non-skin symptoms related to GDS
Abdominal pain
Nausea –emesis
Diarrhea
Weight loss
Headache
Visual alterations
Fever
Myalgias
Arthralgias
Paraesthesias
Haematuria, Menometrorrhagia, gingivorrhagia,
Haematemesis
Nephropathy by immune-complexes
Vasomotor symptoms including syncope
Vertigo