Gardner–Diamond Syndrome

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Definitions

Synonyms

Autoerythrocyte sensitization syndrome
Psychogenic purpura
Painful bruising syndrome
Painful blue spots

Gardner–Diamond syndrome (GDS) is an autoimmune disorder characterized by sensitization to phosphatidylserine of erythrocyte stroma often provoked or exacerbated by stressful events.

This syndrome is named after the American paediatrician Frank H. Gardner and the Russian-American paediatrician Louis Klein Diamond who first systematized the data about psychogenic purpura. However, the first description of this disorder dates back to 1927 when German psychiatrist F. Schindler described 16 patients

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with similar skin haemorrhages. Soon after, another German psychiatrist, E. Jakobi, noted the association of psychogenic purpura with mental disorders (1929).

Epidemiology

GDS is an extremely rare disorder and probably underdiagnosed. Only about 185 cases have been described in the literature by now. These reports come from different countries: Japan, Germany, the United States, India, Turkey, Lebanon, Mexico, France, Norway, Czech, Spain, and Russia. Thus, GDS is considered to be a rare worldwide disorder.

Notably, this disorder is observed almost exceptionally in women, mainly younger than 30 years old. GDS in men, adolescents, and children is unlikely.

Aetiology and Potential Pathogenesis

Theories about the pathogenesis include:

- Originally Diamond suggested that skin lesions in patients treated by Gardner develop due to autosensitization of the patient to some components of his own blood. In 1955 they confirmed this suggestion by skin tests, and concluded that a causative agent is located in the erythrocyte stroma but not in the blood plasma and that it was not associated with haemoglobin.
- Ten years later, Groch et al. (1966) conducted a study to detect the specific substance in the erythrocyte stroma, involved in the development of GDS. They first revealed autosensitization to phosphoglyceride of red blood cells membrane called phosphatidylserine and suggested that it plays a pathogenetic role in GDS.
- Struneck et al. used indirect immunofluorescence and showed that more than 50% of erythrocyte phosphatidylserine of patients with GDS was redistributed on the outer surface of the cell membrane. They successfully induced such redistribution in an experiment after incubation of homologous erythrocytes from a healthy donor with blood plasma of patients, containing specific antibodies of the IgE class to cardiolipin and phosphatidylserine. Some role of immunologic disorders can also be suggested due to the successful treatment of GDS with plasmapheresis in comparison to placebo in one case report.
- Merlen suggested that disturbances in the tonus regulation of venous capillaries due to fluctuations in the kallikrein–kinin system may play an important role in the pathogenesis of GDS. Also, disorders of fibrin synthesis in the endothelium and formation of defective structures of capillary walls were detected as well as extravasation of erythrocytes, carrying sensitizing antibodies.
- Emotional factor may play a determinant role in the pathogenesis of this disease although the mechanisms mediating this association still need to be elucidated. For a long time, GDS was considered as a psychodermatosis, which develops in women with histrionic personality traits. Agle and Ratnoff noted marked emotional lability in patients with GDS and conversional symptoms, coinciding with mental stress. Besides that, some patients from their study suffered from mental disorders and received psychiatric treatment before the development of purpura.

- There are a few observational studies where typical GDS lesions were induced under hypnosis.

It is therefore unclear which mechanisms underlie stress influence on physiological processes in GDS and how it switches the immune system to the synthesis of autoantibodies to erythrocytes.

Although some authors observed gastrointestinal haemorrhages, haematuria, haemarthrosis, intermuscular haematoma and disorders of cerebral blood supply in patients with dermatological symptoms of GDS, the pathologic process is usually confined to skin lesions and not associated with disturbances in the blood coagulation system or abnormalities in vessel development. It was shown that these patients can receive surgical treatment without bleeding complications, although normally surgical interventions are contraindicated in persons with this condition.

There are only sporadic reports about comorbidity of GDS with thrombocytosis, defective thrombocyte aggregation, increase of activated partial thromboplastin time as a result of factor XII deficits, idiopathic thrombocytopenic purpura, and circulating fibrinolytic factor. GDS with haemorrhagic blisters was also reported in patient with alcohol dependence (the GDS features disappeared on cessation of alcohol use).

Clinical Presentation

Dermatologic Manifestations

The development of the disease is usually preceded by slight mechanical injuries, stress, surgical operations, or hard physical work. Sometimes, spontaneous development can be observed. In one case, a copper-containing intrauterine device (IUD) worsened the GDS symptoms. In some patients, the prodromal stage before GDS exacerbation includes general symptoms such as malaise and fatigue. But almost all patients note local burning and stinging sensations, sometimes itch of the skin, just before the development of typical lesions. A few minutes later specific induration of the corresponding skin area appear. The lesions become visible after 4–5 h, when painful oedematous plaques of pink to red in colour and 3–10 cm in diameter develop. The swelling may be severe (Fig. 20.1).

Gradually, the lesions become blueish yellow and, during the next 1–1.5 days, turn into ecchymoses. Erythema and swelling may be present for about 1 day or longer. After the regression of inflammatory infiltration, ecchymoses become less painful, change their colour (blue, greenish and then yellow) and entirely disappear within 7–10 days.

Although the lower limbs, especially on their ventral surfaces, and the trunk are the most often reported localizations of these lesions, they can appear on any other skin area, including the face. Multiple areas may be involved at the same time.

Mental Health Associations

In the majority of publications, mental health associations are considered as an important clinical sign of GDS; their development can be one of the diagnostic criteria of this disorder.

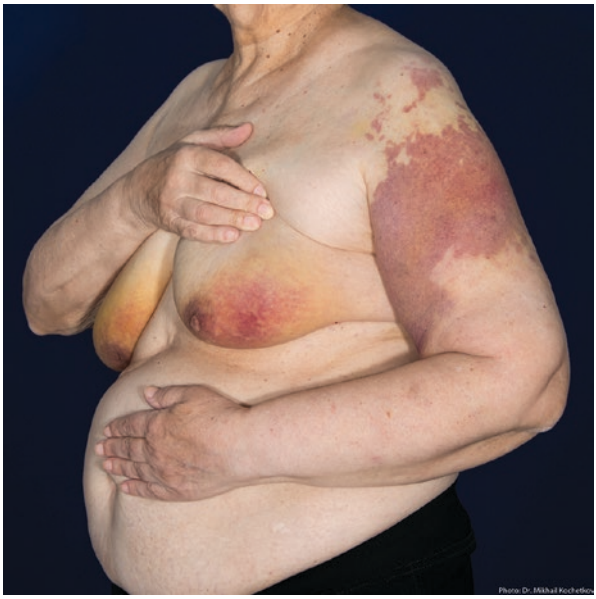

Fig. 20.1 Patient with Gardner–Diamond syndrome. The typical evolution of lesions can be seen: first lesions developed on breasts 2 days prior to the examination and became yellowish; on the left shoulder lesions appeared 1 day prior to the examination and still have a more bright red-bluish colour (photo courtesy of MD, PhD Mikhail Kochetkov)

Psychological Assessment

Many authors state that histrionic personality traits and tendencies to somatic reactions to emotional stimuli are commonly observed in these patients. Psychological examination, sometimes with psychological scales, may show emotional dysregulation.

Psychiatric Examination

According to recent reviews of patients with GDS, co-morbid symptoms of depression are most common (49% of patients), followed by anxiety (16%), personality disorder (4%), conversion disorder (4%), mixed anxiety and depressive disorder (4%), and bipolar disorder (2%). These results correspond to the results of Ratnoff's study who treated the biggest sample of 71 patients with GDS (predominantly women) in the University Hospitals of Cleveland. He also noted the predominance of depressive syndromes in this sample. Some patients also complained about sexual problems and demonstrated histrionic, explosive-dysphoric and obsessive-compulsive behaviour (the terminology for the personality traits was the terminology used at the time of the data publication).

Concomitant Disorders

The development of skin changes can be accompanied by several systemic disorders. Sometimes, the appearance of new skin lesions is associated with fever, arthralgias, myalgias, headaches, and dizziness. More than half of patients with GDS report gastrointestinal symptoms (epigastric pain, gastrointestinal haemorrhages, nausea, vomiting, diarrhoea), which develop simultaneously with the skin lesions. Some authors report haematuria, epistaxis, and menorrhagia. Glomerulonephritis was additionally diagnosed in one patient, and one had a lymphoid interstitial pneumonia. In one case, GDS with

angioimmunoblastic lymphadenopathy was described. Finally, in an original report from Gardner and Diamond, cerebrovascular disease was reported in two cases.

Diagnostic Process

The diagnosis of GDS is based on several clinical and laboratory criteria. An algorithm of examination includes (Table 20.1):

1. Detailed history.
2. Clinical dermatological examination.
3. Laboratory examination (blood count, coagulation parameters).
4. Test with intracutaneous injections of 1 ml of washed autoerythrocytes taken from patient.
5. Psychiatric and psychological examination.

Laboratory Examination

There are no specific laboratory changes in GDS. Haematological parameters are usually within normal ranges (including haemoglobin, haematocrit, platelet counts, peripheral smear, erythrocyte sedimentation rate, electrolytes, bleeding time, prothrombin, thrombin, partial thromboplastin time, factors of coagulation). All other laboratory signs of systemic disorders are usually absent.

The most reliable diagnostic test for GDS consists of an intracutaneous injection of 1 ml 80% suspension of washed erythrocytes obtained from the patient.

The test is positive if the typical for GDS inflammatory lesion develops within 24 h and then gradually progresses into ecchymosis (Fig. 20.2). The test should be made on skin areas the patient cannot access. In some modifications, it is possible to make this test with a suspension of washed autologous leucocytes, minimal quantity of heterologous or autologous DNA and with homologous erythrocytes of a healthy donor.

Table 20.1 Criteria of diagnosis of Gardner–Diamond syndrome

Diagnostic criteria	Comments
1. Typical history.	Episode of physical trauma or stressful event just before the manifestation of GDS, usually in women. A family history of bleeding disorders or platelet dysfunction should be considered.
2. Typical skin lesions.	Inflammatory infiltrated patches and plaques, which turn into painful ecchymoses within 24 h.
3. Parameters of blood count and blood coagulation system.	Usually within normal ranges.
4. Test with intracutaneous injections of 1 ml of autoerythrocytes.	Test is interpreted as positive when typical GDS lesions develop at the injection site in the following day.
5. Most patients with GDS have co-morbid mental health disease.	Depression, anxiety, conversion disorder, bipolar disorder, and personality disorder can be detected

Histopathology

Biopsies of the ecchymotic lesions reveal extravascular erythrocytes in the dermis, oedema, and non-specific lymphohistiocytic infiltration around the blood vessels in the middle and lower layers of the dermis. In macrophages, pigment deposition is observed, which stains positive for iron. In older lesions, subcutal oedema and haemorrhages can be observed. Leukocytoclastic changes in infiltrates or fibrinoid degeneration of vessels are not typical.

In most cases, the histopathological examination is not obligatory (Fig. 20.3).

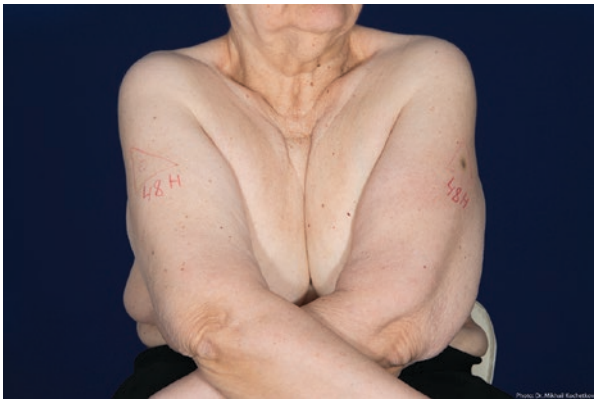

Fig. 20.2 Positive intracutaneous test with own washed erythrocytes: typical ecchymotic lesions are seen on the left shoulder of the patient, whereas on the right shoulder there is no reaction at the place of saline injection (control site) (photo courtesy of MD, PhD Mikhail Kochetkov)

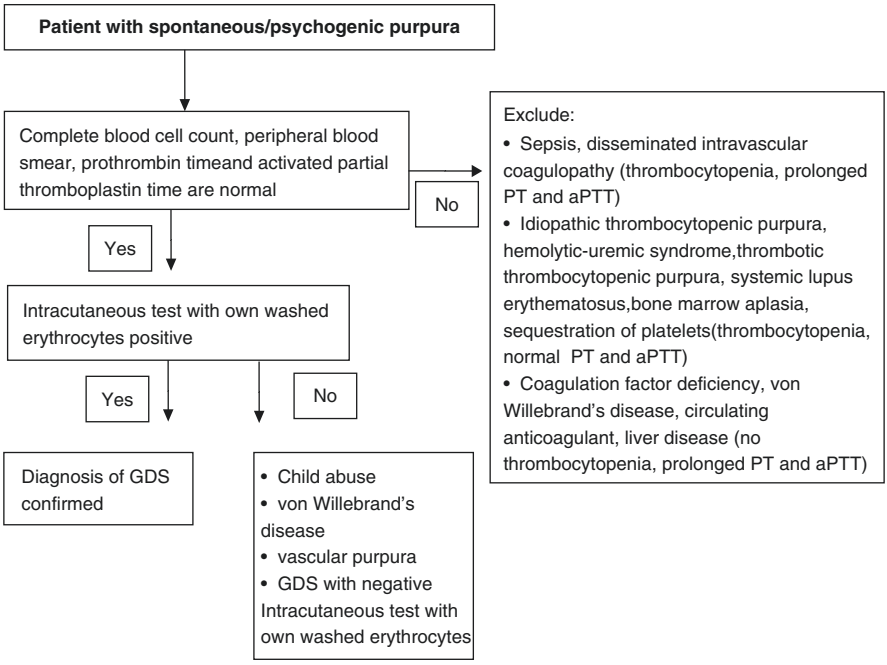

Fig. 20.3 Algorithm for diagnosis of GDS

Differential Diagnosis

Several conditions should be considered as differential diagnosis of GDS (Table 20.2) and should be excluded based on their typical clinical symptoms and laboratory parameters. In some cases, skin biopsy of lesional skin is justified.

Table 20.2 Differential diagnosis of Gardner–Diamond syndrome

Disorder	Distinctive features
Skin manifestations of coagulation disorders (disseminated intravascular coagulation, idiopathic thrombocytopenic purpura, etc.	Typical laboratory changes of blood parameters, history, familial predisposition in idiopathic thrombocytopenic purpura.
Anaphylactoid purpura (Henoch–Schönlein purpura)	This occurs predominantly in children, usually following an infection or medication. The diagnosis is made based on the presence of petechiae (without thrombocytopenia) or palpable purpura that predominantly affects the lower limbs plus at least one of the following four characteristics: abdominal pain; arthralgia or arthritis; renal involvement (proteinuria, red blood cell casts, or haematuria); proliferative glomerulonephritis or leukocytoclastic vasculitis with predominant deposition of IgA on histology.
Polymorphous dermal angiitis	Skin lesions usually have a smaller size and typical histological changes.
Angiitis nodosa	Systemic symptoms (fever, weight loss, myalgias, arthralgias), cutaneous involvement (nodules, livedo, neurologic manifestations, mononeuritis multiplex, peripheral neuropathy, central nervous system, cranial nerve palsy), gastrointestinal tract involvement, abdominal pain, nausea/vomiting, diarrhoea, hematochezia/melaena, hematemesis, oesophageal ulceration, gastroduodenal ulceration, colorectal ulceration, surgical abdomen/peritonitis), urologic and renal involvement (hypertension (recent onset), hematuria, proteinuria, orchitis/epididymitis), ophthalmologic manifestations, cardiac disease, respiratory tract disease pleuritis.
Spontaneous panniculitis (Pfeifer–Weber–Christian disease)	Skin lesions appear as long-existing profound subcutaneous nodes.
Ehlers–Danlos syndrome	In addition to skin ecchymoses, patients have other degenerative stigmas and malformations: excessive distensibility and fineness of skin, hypermobility of joints, muscle hypotonia, eye malformations, etc
Dermatitis artefacta, Münchhausen syndrome	History, clinical presentation (localization and dynamics of lesions) and inconsistent results of intracutaneous test 81–83. Münchhausen requires multiple hospitalizations with the aim to obtain intrusive investigations.
Physical trauma and abuse	History, clinical presentation.

The Course of the Disease

In the majority of patients, relapses and remissions of these lesions may last for many years. The remissions may be long-lasting. In some cases, clinical symptoms of GDS may persist and even worsen. Their severity may fluctuate considerably. The onset of new lesions is mostly seen after physical trauma or stress.

Treatment

Based on the high prevalence of mental disorders and stress reactivity in patients with GDS as well as the absence of coagulation disorders, psychotherapy and psychopharmacotherapy seem to be the most pathogenetically supported treatment modalities. A recent review of 45 patients with GDS reported a 100% success rate in patients receiving selective serotonin reuptake inhibitors (escitalopram, citalopram, and sertraline), and a 96% success rate for talking therapy, which included psychotherapy and reassurance therapy, and a 71% success rate in patients receiving tricyclic antidepressants (desipramine and amitriptyline). When patient management did not include the above-mentioned treatment modalities, the success rate was only 44%. Selective serotonin reuptake inhibitors (SSRIs) and corticosteroids (in combination) may be effective first-line treatments for GDS with proven efficacy in symptomatic relief. GDS refractory to initial treatment may require regular psychotherapy and titrated SSRI dosages to achieve long-term effects. Corticosteroids in isolation are often prescribed and improve symptoms to some extent, but they appear to be less effective than SSRIs. Most of other treatment modalities used in patients with GDS were not effective (Table 20.3).

Table 20.3 Other treatment modalities that were used in patients with GDS

Treatment modalities described in literature	Effectiveness
Cytostatic drugs, hormonal contraceptives, antibiotics, quinolones	Not effective
Busulfan (myelosan)	Effective in a patient with GDS, accompanied by thrombocytosis.
Promethazine	Was more helpful in relieving pain than tramadol
Beta-blockers	Not effective
Bioflavonoids and calcium entry blockers	Not effective
Hypno- and suggestive therapy, psychotherapy	Most effectively improved skin condition as well as mental disorders in young patients

Prognosis

Prognosis for life is favourable.

Practice Point
If you see purpura turning into ecchymoses without significant laboratory changes—ask the patient about stressful and emotionally important events and assess their influence on skin lesions.