Perplexing purpura in two females: Rare case of autoerythrocyte sensitization syndrome

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ABSTRACT

Autoerythrocyte sensitization syndrome is a psychologically induced painful bruising condition. Two female, 19 and 30-year-old presented with recurrent episodes of painful ecchymotic bruising over accessible areas of body. In the younger female, episodes were since 3 years and were precipitated by stress and trivial trauma. The elder female presented with similar lesions since 3 months which were spontaneous in presentation. There were no obvious psychiatric manifestations in either. Clinically, ecchymotic changes in various stages of development were seen. Routine hemogram and coagulation profile were normal. Histopathology showed extravasated erythrocytes, perivascular neutrophils and fibrinoid deposition. Intradermal injection of autologous whole blood produced a painful ecchymotic reaction after 2 h similar to the presenting lesions. Psychiatric evaluation revealed mild mixed depression – anxiety disorder in the younger female while the latter revealed no abnormalities. The diagnosis of autoerythrocyte sensitization syndrome was made based on clinical history and findings, positive autoerythrocyte sensitization test, psychiatric evaluation and absence of any other clinical or laboratory pathology.

Key words: Autoerythrocyte sensitization syndrome, anxiety-depression disorder gardner–diamond syndrome, intradermal test

INTRODUCTION

Autoerythrocyte sensitization syndrome (AES) is an autoimmune vasculopathy with sensitization to phosphatidylserine, a component of erythrocyte stroma. AES usually develops after psychological stress and is characterized by induced or spontaneous development of single or multiple painful inflammatory skin lesions progressing to ecchymoses. We describe two rare cases presenting in females one of them being associated with an underlying psychiatric illness.

CASE REPORTS

Case 1

A 19-year-old female presented with recurrent painful bruises over her extremities since 10 days, the first episode being at age of 16 years. Some episodes followed trivial trauma. She experienced a burning sensation at the injured site few minutes after trivial trauma, with subsequent redness and an appearance of painful bruise lasting for several days. She gave no history of bleeding tendencies or any underlying psychiatric illnesses. Cutaneous examination revealed residual ecchymotic irregular patches, 2 cm × 3 cm on the right arm and the legs, non-tender on palpation [Figure 1]. Rest of mucocutaneous, general and systemic examination was normal. Complete hemogram, platelet count, complete coagulation profile and antinuclear antibodies done to rule out other causes of purpuras were within normal limits. Radiological investigations were normal. Intradermal injection of 0.1 ml of autologous blood on flexure aspect of left forearm caused an immediate burning sensation at the injection site followed 2 h later by development of an oval, 2 cm, sharply defined erythematous macule [Figure 2]. Intradermal injection of 0.1 ml of saline used as a control on the same arm caused no reaction. Biopsy revealed presence of perivascular infiltrate of neutrophils extending up to the septae of the subcutaneous fat [Figure 3]. There was distinctive fibrinoid deposition around the blood vessels. In addition, there were dermal and subcutaneous hemorrhages. The clinico pathological correlation pointed to the diagnosis of autoerythrocyte sensitization syndrome. As
psychiatric associations are frequent, a detailed psychiatric evaluation was done which revealed mixed anxiety depression disorder. Treatment was initiated with tab. Amytriptyline 10 mg and Lorazepam 0.25 mg ½ tab 3 times a day with no new lesions for a week but recurrence of lesions was noted probably secondary to trivial trauma thereafter.

Case 2
A 30-year-old housewife presented with similar spontaneous bruising over upper extremities since 1½ months. There was no prior trauma, menstrual irregularities, or bleeding diathesis. Cutaneous examination revealed multiple ecchymotic patches over bilateral arms, non-tender on palpation [Figure 4]. Hemogram, coagulation profile and radiological studies revealed no abnormalities. The autologous whole blood intradermal injection showed a similar positive reaction as in case 1. Histopathology revealed non-specific changes of extravasation of erythrocytes in lower dermis and subcutis [Figure 5]. Her psychiatric evaluation revealed no abnormalities, however, in view of the diagnosis of AES she was started on tab citalopram 5 mg daily with no new lesions till date.

DISCUSSION
AES also known as Gardner–Diamond syndrome (GDS), painful bruising syndrome, painful blue spots, and psychogenic purpura, is an extremely rare disorder first described by Gardner and Diamond in 1955. Only around 162 cases are described, being reported from Japan, Germany, United States, India,
The exact pathogenesis is not known, but an immunological mechanism has been hypothesized. It is known that in psychological reactions, central nervous system and immune system can modulate these reactions through a two way mechanism. Auto-sensitization of patients to their own blood, mainly to phosphatidylserine (phosphoglyceride of red blood cell (RBC) membrane) plays an important role in the pathogenesis. Struneká et al., showed that more than 50% of the erythrocyte phosphatidylserine of patients with GDS was redistributed on the outer leaflet of the cell membrane. They also found disorder in cytoskeleton organization of RBCs in such patients. Some authors have revealed auto-sensitization to hemoglobin and deoxyribonucleic acid. Merlen suggested that fluctuations in the kallikerin-kinin system lead to disturbance in the tonus regulation of the venous capillaries. Also there is disturbance in the fibrin synthesis in the endothelium, formation of defective structures of capillary walls and extravasation of erythrocytes carrying sensitizing antibodies. There are no disturbances in the blood coagulation system or abnormalities of vessel walls. Though patients with AES can undergo operations without developing major bleeding complications, operations normally are contraindicated in these patients. A number of hematological and immunological abnormalities have been described including thrombocytosis, defective thrombocyte aggregation, increased activated partial thromboplastin time, morphological abnormalities in RBCs, functional platelet defect, idiopathic thrombocytopenic purpura, and abnormally increased tissue plasminogen activator (tPA) dependent cutaneous fibrinolytic activity. Psychological factors play an important role in the pathogenesis. Agle and Ratnoff noted marked emotional liability in the patients coinciding with psychic stress. The exact mechanism how stress influences physiological process and changes immune reactivity so that the organism react with formation of erythrocyte antibody is not clear.

The development of disease usually is preceded by slight mechanical injuries, stress, surgical procedures and hard physical work, though they can develop spontaneously as well.

There may be a prodrome stage consisting of malaise, fatigue etc., Lesions develop stereotypically with initial burning or stinging sensation, followed 4-5 h later by development of painful edematous indurated and erythematous plaques of 3-10 cm. Subsequently, the lesions become blue and in 1-2 days turn ecchymosed with annular spread. The erythema and edema may be present for one or more days. Soon the inflammatory infiltrate regresses and ecchymoses become less painful and change from blue to green and then finally yellow, and disappear entirely in 7-10 days. Lesions are most commonly located over the arms, trunk and legs. However, multiple areas can be involved at the same time. Some may also present as cellulitis or even bullous lesions. Appearance of new lesions may be associated with fever, arthralgias, myalgias, headache, and dizziness. Furthermore, other symptoms such as epistaxis, gastrointestinal hemorrhages, hemorrhosis, menorrhagia, hematuria, and intracranial bleed have been reported. Glomerulonephritis in addition to AES has also been reported.

Ratnoff and Agle pointed out occurrence of mental insufficiency in AES. Psychopathological disorders observed are hysterical personality traits, egoistic characters, emotional liabilities, self-injuries, difficulty in suppression of aggression, depression, “aphonia,” “paralysis,” “paresthesia,” dissociative disorders with “convulsions,” “hallucinations,” and “syncope.” Ratnoff in a large study of 71 patients found that depressive symptoms predominated. However, in some cases, no specific predominant psychopathological syndrome may be seen.

The diagnosis is based on the typical clinical and laboratory characteristics as summarized in Table 1. There are no specific

| Table 1: Clinical and laboratory characteristics of patients with Gardner–Diamond syndrome |
|---------------------------------------------------------------|
| Patients are mainly women                                     |
| Typical anamnesis (psychical stress and/or physical trauma, preceding the disease onset) |
| Typical eruptions: Oedematous erythema evolving to the painful ecchymoses during 24 h |
| General symptoms (fever, arthralgia, etc.) are not obligatory |
| Frequent association with psychological disorders             |
| Positive intracutaneous test with autoerythrocytes             |
| Coagulogram is normal                                          |
| Histopathological findings are not specific                   |

Turkey, Mexico, France, Norway, Czech, and Spain. It occurs exceptionally in women aged 19-72 years. Disease in men and children also have been described.
laboratory changes in GDS. Hematological parameters, coagulation profiles are usually within normal limits and laboratory signs of systemic disorders are also absent.[1] An intracutaneous injection of 1 ml 80% suspension of autologous washed erythrocytes is a reliable diagnostic test for GDS.[16]

The test is positive, if typical GDS inflammatory lesion develops within 24 h, and gradually progress to form ecchymosis. Modifications to this test with a suspension of washed autologous leucocytes, minimal quantity of heterologous or autologous DNA and with homologous erythrocytes of a healthy donor have also been possible. Histological evaluation is not obligatory as biopsy of the early lesion shows edema and moderate mononuclear infiltrate in upper dermis and late lesions shows extravasated erythrocytes in the dermis without infiltrate.[1]

The differential diagnosis of GDS should include skin manifestations of coagulation disorders, anaphylactoid purpura, polymorphous dermal angitis, angitis nodosa, spontaneous panniculitis, Ehlers–Danlos syndrome, compartment syndrome, and cellulitis. Solitary cases following primary manifestation of systemic lupus erythematosus and a copper-containing intra uterine device have also been described. Dermatitis artefacta can be ruled out by anamnesis, clinical presentation, and inconsistent results of intracutaneous test. Banal beating and Munchausen’s syndrome must also be ruled out.[19]

Prognosis is of GDS is generally good with no reported fatalities. In the majority of patients, remissions and relapses may last for as long as 38 years.[6] The remissions may be long-lasting. In some cases, clinical symptoms of GDS may persist and even worsen. Its severity may considerably fluctuate. The onset of new lesions is most probable after physical trauma or stress.

Treatment of GDS is still problematic (dermatosis sine therapia) as no method of treatment is sufficiently effective in this disease. Glucocorticoids, cytostatic drugs, hormonal contraceptives, antibiotics, quinolones are not effective; their effect is similar to placebo.[17] Though there is no satisfactory treatment of GDS, plasmapheresis, psychotherapy, and oral cyproheptadine have been successfully tried in isolated cases.[18,19]

In general, it is not difficult to make the diagnosis of GDS, though these patients require certain period of observation to exclude artificial origin of lesions. Positive intracutaneous test is a very useful tool to support the diagnosis.[20] Positive psychic disorders and dependence of lesions development from stress along with absence of hematological disorders and specific changes by histological examination will help to make the correct diagnosis. This condition should be kept as a differential diagnosis of recurrent painful purpura. Timely and correct diagnosis helps to avoid exhaustive investigations and aggressive treatment.

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