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A SEVERE FORM OF GARDNER-DIAMOND SYNDROME IN A PATIENT WITH SCHIZOPHRENIA: A RARE COMORBIDITY WITH AN EXCEPTIONAL PATHOPHYSIOLOGY

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INTRODUCTION

Gardner-Diamond Syndrome (GDS), also known as psychogenic purpura or autoerythrocyte sensitization syndrome, is a rare cutaneous disorder characterized by recurrent, atraumatic, spontaneous ecchymosis that is mostly seen in the extremities. The condition usually occurs spontaneously after emotional distress. GDS is a diagnosis of exclusion and primarily based upon the clinician suspecting the presence of the disorder, after ruling out coagulopathies and bleeding diathesis. Although pathophysiological abnormalities associated with psychiatric undertones were proposed as the underlying mechanisms (Ratnoff 1989), the exact etiopathogenesis of the disease remains unknown. To date, various pre-existing psychiatric diagnoses have been reported in GDS patients (Block et al. 2019); however, the comorbidity of GDS and schizophrenia has never been reported. Here, we present the case of a patient with schizophrenia who developed a severe form of GDS and aim to highlight the putative pathophysiology that can explain the co-existence of both disorders.

CASE PRESENTATION

A 45-year-old male patient was diagnosed with schizophrenia 15 years previously, and was being treated for the past 12 years at our forensic psychiatry inpatient unit with a compulsory treatment order. The patient was being treated with p.o. amisulpride 800 mg/day, risperidone 8 mg/day, mirtazapine 15 mg/day and haloperidol decanoate i.m. 150 mg/month with no change in the treatment regimen in the past year. Three months previously, progressive ecchymosis was observed to start abruptly on the patient's right lower leg. The patient, who had normal vital signs and no preceding nor a concomitant history of physical trauma, injury or infection, stated that the lesions were heralded by a burning sensation and progressed to a tender, bluish-red, non-edematous ecchymosis that was approximately 10x5 cm in diameter, located on his right knee. The lesion had multiplied and spread through to the distal and proximal parts of the limb a week later.

A detailed laboratory screening, including a hemogram, liver/renal functions and toxicology panels, was carried out upon the progression of lesions; all results were found to be within the normal range. The patient's hemoglobin level was 11.8 *g/dL* (*n*:12-16 *g/dL*), and platelet count was 185000/μL (*n*:150000-400000/*μL*). Coagulation parameter analyses including INR, PT, aPTT were found to be non-significant. Further hematological evaluations in a stepwise fashion revealed normal primary and secondary hemostasis. The patient reported the absence of any history of bleeding disorders or familial hematological disorders. Malingering and factitious disorder were also ruled out after careful examination and close observation. The current antipsychotic medications were tapered off and finally ceased to exclude any possible late-onset drug-related side effects. Over the subsequent days, the ecchymoses was observed to progress further and covered both lower extremities (Figure 1). Meanwhile, a follow-up hemogram revealed a severe decrease in hemoglobin to 5.1 *g/dL* without any observable hemorrhage. Brain, thorax and abdomen CT scans as well as endo-colonoscopy were performed to exclude any internal bleeding; all outcomes were normal. Genetic and pathologic examinations of a bone marrow biopsy specimen did not suggest severe anemia. Prednisolone 60 mg/d p.o. was empirically initiated; however, no response in the hemoglobin levels was recorded. During the follow-up, the patient developed symptoms of refractory anemia and hypovolemia including hypotension, fatigue, malaise and loss of appetite, and required a total of 13 units of erythrocyte transfusion within fifteen days. Leukocyte and platelet counts remained within the normal range. Autoantibodies, serology and rheumato-inflammatory marker evaluations suggested that these parameters were non-contributory. A punch biopsy of the skin lesions showed non-specific extravasated erythrocytes throughout the dermis but no evidence of vasculitis. In view of the findings, GDS was suspected and an intradermal skin test was performed with washed autoerythrocytes. Typical ecchymotic lesion were observed at the injection site within 12h, which supported the diagnosis of GDS. A

psychiatric examination revealed that although the patient was under remission for psychotic symptoms, he had appeared preoccupied with the reduced interest in his family members in the last months and was frustrated with his current medical condition. A previous Minnesota Multiphasic Personality Inventory (MMPI) test had revealed high hypochondriasis and neuroticism.

Since a psychogenic origin was considered in the etiology of GDS in the current patient, p.o. risperidone 6 mg/day was combined with escitalopram 10 mg/day along with motivational interviews and brief supportive psychotherapy sessions thrice a week. Three weeks later, the ecchymosis patches began to resolve and hemoglobin remained stable (12.4-12.7 *g/dL)* in weekly follow-up screenings. The patient's anxiety symptoms showed amelioration and clinical improvement was confirmed with a decrease in the Hamilton Anxiety Scale score from 26 to 14, while the Brief Psychiatric Rating Scale score decreased from 29 to 18. The patient is currently under maintenance treatment at our inpatient unit and remains symptom-free.

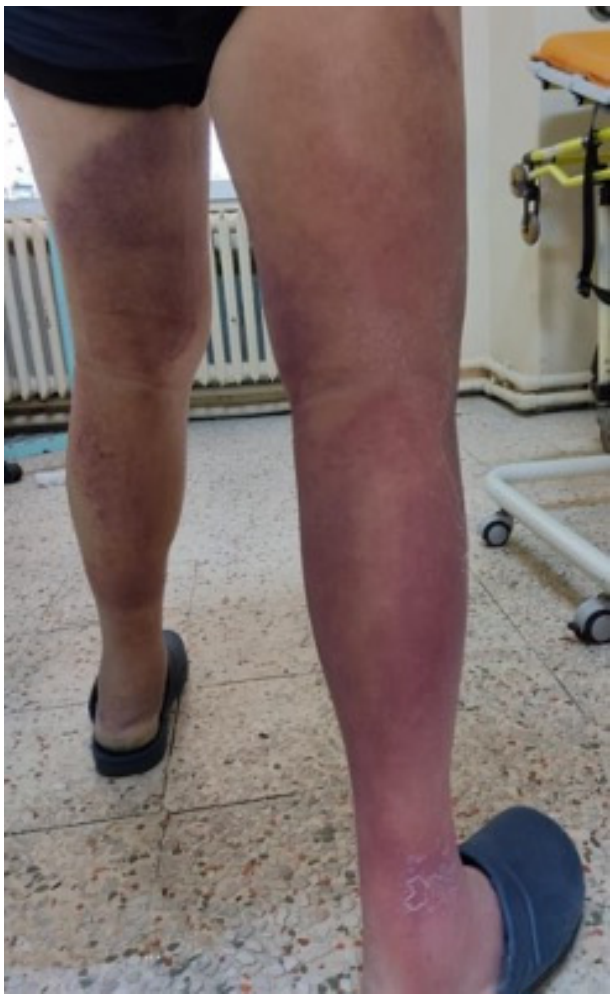

Figure 1. Widespread ecchymotic patches in both lower extremities

DISCUSSION

Approximately half of GDS patients were reported to have an underlying psychiatric diagnosis including depressive and anxiety disorders (Sridharan et al. 2019). However, to our knowledge, the current case study is the first to report the comorbidity of GDS with schizophrenia. Psychosocial stressors are implicated in the occurrence of symptoms in 40-60% of reported patients (Park et al. 2016). This may explain the development of lesions in the current patient who had recently undergone increased levels of anxiety due to familial conflicts. Contrary to the observations in the current study, GDS lesions were previously reported to be benign in nature and spontaneously resolve within one-or-two weeks. Therefore, the longer duration of the disorder and GDS-related severe anemia in the current patient were remarkable, which may indicate that patients with schizophrenia are more prone to develop aggravated psychoimmune stress reactions. Furthermore, the current report also highlights the importance of considering the incidence of GDS in middle-aged males, an affliction that is most often seen in middle-aged women (Ivanov et al. 2009).

It is likely that highly complicated temporal interrelations exist between psychogenic alterations and GDS. Investigation of potential psychopathologies, in particular, distal or proximal psychic stress coinciding with personality traits along with prominent emotional lability is key in the diagnosis of GDS. Several factors may account for how psycho-emotional distress can alter hemostatic equilibrium to the point where intradermal bleeding occurs and how schizophrenia might contribute towards the development of GDS. Previous research has consistently reported that phosphatidylserine, a component of the erythrocyte stroma, has an atypical cellular organization in GDS, and stress-related autosensitization to phosphatidylserine is one of the main causes of the disorder (Ivanov et al. 2009; Jafferany & Bhattacharya 2015). Ponizovsky et al. reported that psychotic patients can show alterations in the composition of erythrocyte membrane phospholipids (Ponizovsky et al. 2001). Other mechanisms include tonus dysregulation of venous capillaries that may be related to fluctuations in the kallikrein-kinin system (Ivanov et al. 2009). The kinin activity is known to oscillate in response to emotional stimuli (Sridharan et al. 2019); moreover, increased activity of the kallikrein-kinin system has been reported in schizophrenia (Black & Garbutt 2002). Imbalances in catecholamine levels and the HPA-axis, which are well-recognized in the pathophysiology of schizophrenia, were suggested to contribute to the hemostatic disparity observed in GDS through altered site-specific tPA and local plasmin activity (Jafferany & Bhattacharya 2015). Finally, psychological stress may also lead to a compromise in vascular endothelial integrity (Black & Garbutt 2002), and endothelial dysfunction has been demonstrated in schizophrenia (Dieset et al. 2015).

CONCLUSION

Although GDS is sometimes considered to be an autoimmune vasculopathy, researchers are often reluctant to describe it as a quintessential inflammatory disease, and anti-inflammatory drugs are usually not effective (Cansu et al. 2008). The current patient was also observed to not respond to corticosteroids. Combination or monotherapy of SSRIs (particularly escitalopram, citalopram, and sertraline) and psychotherapy were suggested to have favorable outcomes with alleviated symptoms in more than 90% of patients (Block et al. 2019). The current report also highlights the fact that exhaustive laboratory investigations and belated diagnosis may worsen ongoing symptoms by exacerbating the patient's frustrations. Therefore, an early suspicion of the disorder and prompt initiation of appropriate psychiatric treatment in GDS can substantially benefit the patient.

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