

# First presentation of Sneddon-Wilkinson disease with unexpected immunoglobulin A gammopathy: A case report and review of the literature

SAGE Open Medical Case Reports  
JCMS Case Reports  
Volume 7: 1–4  
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DOI: 10.1177/2050313X19826432  
journals.sagepub.com/home/sco



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## Abstract

We present a case of Sneddon-Wilkinson disease in a 52-year-old female at her first presentation to dermatology. Outlined in the case are various investigations undertaken at this initial presentation, including rheumatologic and hematologic malignancy markers, which identified immunoglobulin A gammopathy. The systemic and topical therapies used to treat the patient's condition are described, as well as her response to these treatments. In this discussion, we explain the epidemiology, pathophysiology, and clinical presentation of Sneddon-Wilkinson disease. Various medical conditions having known association with Sneddon-Wilkinson disease are discussed, including immunoglobulin A or immunoglobulin G monoclonal gammopathies and lymphoproliferative disorders. A comprehensive differential diagnosis for Sneddon-Wilkinson disease is provided, including immunoglobulin A pemphigus, acute generalized exanthematous pustulosis and pustular psoriasis, among others. We describe the systemic and topical therapy options for the treatment of Sneddon-Wilkinson disease, of which first line treatment is systemic dapsone. This patient serves as an excellent case of Sneddon-Wilkinson disease with unexpected immunoglobulin A gammopathy.

## Keywords

Dermatology, hematology, oncology, rheumatology, case report

## Introduction

A 52-year-old female presented with a 3-week history of pustular skin lesions affecting the shoulders, axillae, and flanks, as well as a “burning” skin sensation. The patient's clinical presentation was concerning for subcorneal pustular dermatosis (SPD), which is characterized by waves of isolated or grouped flaccid pustules measuring several millimeters with potentially underlying erythematous skin,<sup>1</sup> generally found on the trunk and intertriginous areas.<sup>2</sup> Described are the various investigations undertaken in the workup of this patient that ultimately uncovered an unexpected immunoglobulin A (IgA) gammopathy.

## Case

A 52-year-old female presented to clinic for a skin eruption for 3 weeks with a primary complaint of skin “burning” in the affected areas, which she treated with diphenhydramine and cetirizine. She endorsed a history of unintentional weight loss, but denied night sweats, joint pain, and pleuritic pain.

Her medical history included cirrhosis and chronic pain. She denied any personal history of dermatologic conditions, however endorsed family history of psoriasis.

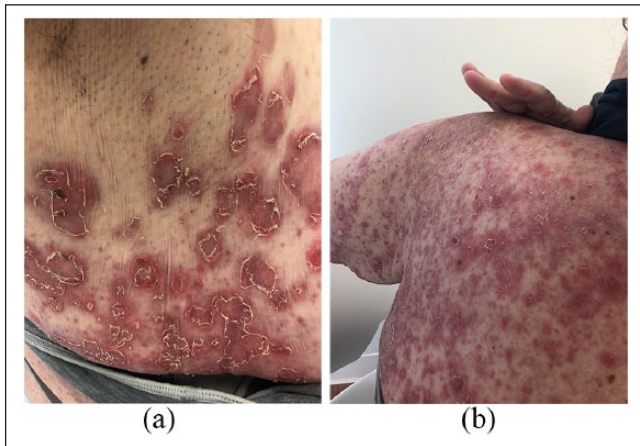
On examination, there were multiple erythematous papules and pustules to the flanks, shoulders, axillae, and upper arms (Figure 1). The pustules were flaccid and demonstrated fluid levels. There were also desquamated areas, which exhibited geographic and serpiginous borders. Two punch biopsies were done of the affected area on the left shoulder. Numerous investigations to rule out associated hematologic or rheumatologic disorders were ordered, which included as follows: anti-nuclear antibody (ANA), rheumatoid factor (RF), IgA level, protein electrophoresis panel, extractable nuclear antibody (ENA) panel (including anti-Ro, anti-La, anti-Smith, and anti-ribonucleoprotein antibodies), and

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**Figure 1.** (a) Patient's right axilla at initial presentation and (b) patient's left shoulder at initial presentation.

anti-skin antibody panel (including basement membrane antibody and intercellular antibody). The patient was started on dapsone 100 mg PO daily as treatment for suspected SPD. Appropriate monitoring bloodwork for dapsone treatment was ordered, including a glucose-6-phosphate dehydrogenase (G6PD) screen; complete blood counts (CBCs); and renal and hepatic function monitoring. An acute hepatitis panel was ordered for hepatitis A, B, and C.

The ANA (negative at 1:80), RF ( $<10.0$  IU/mL), ENA, and anti-skin antibody panels (negative at 1:10) were all negative. The IgA level was elevated (4.67 g/L). Protein electrophoresis showed elevated protein (87 g/L), alpha-2-globulin (10.7 g/L), beta globulin (13.7 g/L), and gamma globulin (15.1 g/L). Albumin and alpha-1-globulin levels were normal. The hepatitis panel and G6PD screen were negative. The baseline creatinine was elevated (105  $\mu$ mol/L). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were normal. The CBC demonstrated normal hemoglobin (114 g/L), an elevated leukocyte count ( $15.74 \times 10^9$ /L) with elevated neutrophils ( $11.07 \times 10^9$ /L), and elevated platelets ( $482 \times 10^9$ /L).

The histological report of the punch biopsies indicated superficial perivascular dermatitis and subcorneal pustules, consistent with SPD. Histological features suggesting psoriasis were not identified. Additional review of the biopsies elicited a broad differential, including bullous impetigo, acute generalized exanthematous pustulosis, pustular psoriasis, IgA pemphigus, SPD, and amicrobial pustulosis of the folds. Given the patient's clinical presentation, and autoimmune and hematologic malignancy markers, a working diagnosis of SPD was assumed.

An urgent referral to hematology was made for further investigation of potential hematologic malignancies, including IgA monoclonal gammopathy, and multiple myeloma.

After 1 month, the patient demonstrated clinical improvement in the affected areas with dapsone treatment. A disease flare occurred one day after surgery, and

triamcinolone acetonide cream 0.1% was prescribed. Additional investigations obtained at this time demonstrated normal calcium and immunoglobulin G (IgG) levels, low immunoglobulin M (IgM; 0.26 g/L), persistently elevated IgA (3.68 g/L), elevated free kappa light chains (22.83 mg/L), and normal free lambda light chains. After 6 weeks, follow-up showed well-controlled disease on dapsone 100 mg PO daily and topical steroid treatment as needed.

## Discussion

SPD, or Sneddon-Wilkinson disease, is a chronic relapsing vesiculopustular eruption typically seen in female after the fourth decade. Cutaneous lesions are generally found on the trunk and intertriginous areas, and pustules may coalesce to form circinate patterns.<sup>2</sup> Because of potential misdiagnosis of the disorder and its rare incidence, there is no estimate of the prevalence of SPD, and there is no evidence of a particular geographic distribution of the disease.<sup>3</sup>

Histologically, SPD is a sterile eruption caused by subcorneal accumulation of neutrophils. SPD's key clinical features are very unique and integral to making the diagnosis; the primary lesions consist of waves of isolated or grouped flaccid pustules measuring several millimeters with underlying potentially erythematous skin. As seen in our patient, the lesions may demonstrate fluid levels, whereby sterile pus accumulates in the lower half, with overlying clear fluid. The pustules generally coalesce and may form annular, circinate, or serpiginous patterns. The pustules are easily ruptured by friction, especially in the body folds. Areas of involvement generally include the axillae, groin, neck, submammary regions, and their adjacent skin; involvement of the palms, soles, mucous membrane, and face are atypical. Local irritation or itch of the affected areas may be present, however systemic symptoms are uncommon. Rupture of the pustules produces a superficial scale, and as the eruption resolves, mild hyperpigmentation may develop, over which further pustules may arise.<sup>1</sup>

SPD may initially occur without association of an underlying malignancy; however, these patients should be followed up for prospective malignancies because of the strong association between the two.<sup>4</sup> SPD is frequently associated with various forms of immune dysfunction, namely, IgA or IgG monoclonal gammopathies and lymphoproliferative disorders (especially multiple myeloma).<sup>1</sup>

The majority of reports of immune dysfunction associated with SPD have been of IgA monoclonal gammopathies with either kappa or lambda light chain type,<sup>5</sup> which our patient with an elevated IgA level and elevated free kappa light chains falls under. There appears to be a relationship between IgA monoclonal gammopathy and SPD due to the fact that neutrophils possess receptors for IgA. In addition, there are reports that increased serum IgA correlates with inhibition of neutrophil chemotaxis,<sup>6</sup> as does the presence of IgA paraproteins.<sup>7</sup>

**Table 1.** Various laboratory markers and their normal reference ranges in the Saskatoon Health Region.

Laboratory marker	Normal reference range
Leukocytes	4.00–11.00 × 10 <sup>9</sup> /L
Hemoglobin	110–160 g/L
Platelets	150–400 × 10 <sup>9</sup> /L
Creatinine	45–90 µmol/L
Alanine aminotransferase (ALT)	5–45 U/L
Aspartate aminotransferase (AST)	10–35 U/L
Rheumatoid factor (RF)	0.0–20.0 IU/mL
Protein	60–80 g/L
Albumin; gel electrophoresis	39.0–51.0 g/L
Alpha-1-globulin; gel electrophoresis	2.0–4.0 g/L
Alpha-2-globulin; gel electrophoresis	4.0–8.0 g/L
Beta globulin; gel electrophoresis	5.0–10.0 g/L
Gamma globulin; gel electrophoresis	6.0–12.0 g/L
IgA	0.40–3.50 g/L
IgG	6.50–16.00 g/L
IgM	0.50–3.00 g/L
Total calcium	2.10–2.55 mmol/L
Free kappa light chains	3.30–19.60 mg/L
Free lambda light chains	5.60–26.30 mg/L

IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M.

Other immunologic conditions that have shown association with SPD include IgG monoclonal paraproteinemia,<sup>8</sup> multiple myeloma,<sup>9</sup> and possibly an IgM monoclonal band.<sup>10</sup> In addition, other medical disorders have been noted in association with SPD including pyoderma gangrenosum,<sup>11</sup> systemic lupus erythematosus;<sup>12</sup> seropositive<sup>10</sup> and seronegative<sup>13</sup> rheumatoid arthritis; Crohn's disease and ulcerative colitis;<sup>14</sup> synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome;<sup>15</sup> hyperthyroidism;<sup>16</sup> hypothyroidism;<sup>17</sup> apudoma;<sup>18</sup> and polycythemia rubra vera.<sup>17</sup>

The differential diagnosis for SPD is quite broad and encompasses many variables including clinical presentation, histopathological features, and laboratory markers (Table 1). The main cutaneous disorders to be considered include IgA pemphigus, pemphigus foliaceus, annular pustular psoriasis, generalized pustular psoriasis of pregnancy, pustular psoriasis—other localized and generalized forms, acute generalized exanthematous pustulosis, bacterial impetigo, dermatophytosis, dermatitis herpetiformis, and necrolytic migratory erythema.<sup>1</sup> Generally, a thorough medical history (encompassing history of presenting illness, drug exposures, and past medical history), physical examination, and histopathology can significantly narrow the differential diagnosis. Immunofluorescence staining can be helpful in distinguishing SPD from various immunobullous disorders.

Traditionally, SPD has been challenging to differentiate from pustular psoriasis. Clinically, pustular psoriasis tends to present with more systemic involvement than SPD. Patients

with pustular psoriasis may present with fever, severe malaise, and neutrophilia, while SPD patients do not generally present with fever or systemic toxicity.<sup>1</sup> On examination, pustules of psoriasis are smaller (pin-head sized) than SPD pustules, but later may coalesce to form lakes of pus. They are located mainly at the periphery, thus forming a pustular margin.<sup>19</sup>

Histologically, in SPD, spongiform changes are not seen in the base or edge of the pustule.<sup>20–22</sup> In pustular psoriasis, the classical histological features of psoriasis may or may not be present; however, the aforementioned spongiform changes are present, thus making them a key discriminating feature between the two conditions.<sup>19</sup>

With regard to treatment of SPD, dapsone is the treatment of choice, generally at a dose of 50–200 mg PO daily. Once disease control has been obtained, the dose may be tapered to achieve the minimum effective dosage required. Other alternatives to dapsone include sulfapyridine and sulfamethoxypyridazine; however, these have been noted to be less effective in general.<sup>1</sup> Other reported treatment options described in the literature include etretinate<sup>23</sup> (also in combination with dapsone<sup>24</sup>), acitretin,<sup>25</sup> narrowband (TL-01) UVB, PUVA, re-PUVA,<sup>25</sup> broadband UVB,<sup>26</sup> colchicine,<sup>27</sup> cyclosporine,<sup>28</sup> and infliximab.<sup>29</sup> Oral corticosteroids are usually employed to help treat an associated condition, such as pyoderma gangrenosum, multiple myeloma, or systemic lupus erythematosus.<sup>1</sup> Potent topical corticosteroids may also be used as treatment alone<sup>30</sup> or in conjunction with dapsone.<sup>2,31</sup>

In summary, our patient was an example of SPD with unexpected IgA gammopathy. As illustrated in our case, investigations at first presentation should include rheumatologic and hematologic malignancy markers, as well as any other clinically relevant investigations. Skin biopsy of the lesions is also critical in obtaining the diagnosis; skin biopsies for immunofluorescence testing may also be indicated. Once the diagnosis has been made, patients should be started on first-line dapsone treatment. If any underlying rheumatologic or hematologic conditions are identified, appropriate referral to the respective specialists should be initiated. Last, patients in whom underlying medical conditions are not identified should have regular medical follow-up for the development of potential future malignancies.

#### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

#### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Informed consent

Verbal informed consent was obtained from the patient. The patient has read the case report and feels her perspective is included in the writing.

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