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REVIEW ARTICLE

Drug-Induced Pyoderma Gangrenosum: A Review

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Abstract Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that may be caused by an adverse drug reaction. We discuss the clinical presentation and outcomes of 52 cases of drug-induced PG reported to date in the literature. We conducted our literature search for case reports of drug-induced PG using keywords on PubMed and Medical Subject Heading (MeSH) terms on MEDLINE and EMBASE. To assess the probability that each case of PG was related to drug therapy, we used the Naranjo criteria. We identified 44 studies in the literature, with a total of 52 cases of drug-induced PG. The mean Naranjo score for cocaine-induced PG ($n = 13$) was 9.4, indicating a definite adverse drug reaction, while the mean Naranjo scores for isotretinoin ($n = 5$), propylthiouracil ($n = 5$), and sunitinib ($n = 5$) were 6.2, 6.8, and 7.4, respectively, indicating probable adverse drug reactions. Drugs should be considered as a possible triggering event whenever PG is diagnosed, and clinicians should particularly consider this in patients taking isotretinoin, propylthiouracil, or sunitinib, as well as in patients with a history of cocaine use.

Key Points

Cocaine-induced pyoderma gangrenosum (PG) is a definite adverse drug reaction.

PG associated with isotretinoin, propylthiouracil, and sunitinib is a probable adverse drug reaction.

Onset can be years after a drug is started and there is no specific clinical or pathological pattern that suggests drug-induced PG.

1 Introduction

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis. It is characterized by painful, sterile ulcers, often occurring on the lower legs and trunk, and most cases occur in adults aged 30–50 years [1]. PG is polygenic and autoinflammatory in nature [2]. There is overexpression of interleukin (IL)-1β, IL-17, tumour necrosis factor (TNF)-α, and multiple chemokines, which supports the mechanism of neutrophil activation and migration [2, 3]. Genetic analysis in PG has shown mutations in several known autoinflammatory genes, including MEFV and PSTPIP1 [2].

In 50% of cases, PG is associated with underlying disease, most commonly inflammatory bowel disease (IBD), rheumatoid arthritis, myelodysplastic syndrome (MDS), or haematologic malignancies [1, 4]. There are four major clinical variants of PG: ulcerative, pustular, bullous, and vegetative, with ulcerative being the most common by far [4]. Treatment is focused on immunosuppression.

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Drug-induced PG is a rare adverse cutaneous drug reaction and its diagnosis can be challenging. Drugs that have been implicated to date are propylthiouracil, granulocyte colony-stimulating factor (G-CSF), and sunitinib [4, 5]. In this review, we discuss the clinical presentation and outcomes of 52 cases of drug-induced PG reported to date in the literature.

2 Methods

We conducted our literature search for case reports of drug-induced PG using keywords on PubMed, and Medical Subject Heading (MeSH) terms on MEDLINE and EMBASE. We then used snowballing and forward citation tracking of selected articles to identify additional relevant studies.

We included articles where a diagnosis of PG was made either based on clinical suspicion alone or with the aid of biopsy. Articles were excluded if there was a high clinical suspicion of alternative diagnoses, such as Sweet's syndrome, unspecified neutrophilic dermatoses, or autoimmune vasculitides. Two articles were not available in the English language and one article was not available through our institution's library system [6–8]. In these three cases, we extracted data from abstracts.

To assess the probability that each case of PG was related to drug therapy, we used the Naranjo criteria (Table 1) [9]. Two reviewers each independently scored half of the cases and then checked each other's scores. Any discrepancies were discussed with the primary investigator. For question 1, we scored 'yes' only if there were other conclusive reports of that particular drug implicated in PG, and not other drugs within the same class; for question 3, we scored 'no' if the lesions did not improve with discontinuation of the suspected drug or did not respond to systemic corticosteroids; for question 5, we scored 'yes' if any of the following associated diseases were present: MDS, any haematologic malignancy, rheumatoid arthritis, or IBD; and for question 7, we scored 'yes' if the drug was detected in body fluids in any concentration as there are presently no data to support dose dependence of drug-induced PG.

According to the Naranjo criteria, a score of 1–4 indicates a possible adverse drug reaction, a score of 5–8 indicates a probable adverse drug reaction, and a score of 9–13 indicates a definite adverse drug reaction.

3 Results

We identified 44 case reports (or case series) in the literature, with a total of 52 cases of drug-induced PG (Table 2). The majority of investigators used biopsy to support their diagnosis or to exclude other causes. In only five reports, diagnosis was made based on clinical examination and history alone [10–14]. Su et al. developed guidelines for the diagnosis of ulcerative PG, in which two major criteria and two of four minor criteria must be met [15]. The two major criteria are morphology consistent with PG and exclusion of other causes, while the four minor criteria are pathergy or cribriform scarring, systemic disease associated with PG, histopathologic findings, and response to immunosuppression [15]. Of the 50 cases of ulcerative PG, 35 met these criteria, 10 did not [10, 11, 13, 14, 16–21], and there were insufficient diagnostic data in 5 cases [6–8, 22, 23]. Two cases were bullous PG [24, 25].

For all drugs, with the exception of cocaine, none of the investigators attempted to administer placebo, or to measure serum or urine drug levels; therefore, there was a ceiling Naranjo score of 11 for all prescription therapeutic drugs.

Our study identified only two drugs reported in the literature indicating definite adverse drug reactions (mean Naranjo score 9–13), i.e. cocaine and imatinib, and 13

Table 1 Naranjo Adverse Drug Reaction Probability Scale [9]

Question	Yes	No	Don't know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event occur after the suspected drug was administered?	+2	−1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	−1	0
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	−1	+2	0
6. Did the reaction reappear when a placebo was given?	−1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

Table 2 Cases of drug-induced PG reported in the literature

Author, year	Age and sex	Dose and route	Indication for drug	Initiation of drug to PG onset	Location of lesions	Risk factors for PG	Rechallenge	Naranjo score	Comments
Adalimumab									
Stichenwirth et al., 2008 [23]	42 F	40 mg SC every other week	Rheumatoid arthritis	18 months	Right cheek, right shoulder, left upper arm	Rheumatoid arthritis	No	2	
Alitretinoin									
Levy et al., 2016 [18]	45 F	30 mg PO daily	Eczema	5 months	Lower left leg		Yes; lesions appeared at same site 5 weeks after restarting drug	8	
Azacitidine									
Tseng et al., 2015 [49]	66 F	NR	Myelodysplastic syndrome	3 days into second cycle	Lips, inner nose, upper arms, forearms	Myelodysplastic syndrome	Yes; ulcers recurred on rechallenge	5	
Ciprofloxacin									
Kumaresan et al., 2006 [50]	22 M	500 mg PO bid	Fever	2 days	Upper and lower limbs		No	6	Joint pain also present
Cocaine and levamisole (mean Naranjo = 9.4)									
Baliu-Piqué and Mascaró, 2016 [46]	40s F; exact age NR	NR	Substance abuse	NR	Breasts, hips and all four limbs	Previous PG 3 years ago, on scar tissue	Yes; flares after hospital discharge and on weekends (urine + ve for cocaine)	10	
Jeong et al., 2016 [47]	$n = 8$; ages NR	NR	Substance abuse	<1 week to 4 weeks (median: 1 week)	Lower limbs ($n = 8$), upper limbs ($n = 6$), trunk ($n = 3$), face, nose, ear		Yes; recurred with repeat cocaine use	10	
Jiménez-Gallo et al., 2013 [20]	54 F	3.5 g/ week × 5 years	Substance abuse	5 years	Both legs		Yes; increasingly severe episodes with resumption of cocaine	9	Developed Wegener's granulomatosis-like syndrome at the same time
Keith et al., 2015 [48]	51 F	NR	Substance abuse	NR	Forehead, torso, back, abdomen, thighs, fingers		Yes; new eruption 1 week after repeat cocaine use	9	
Roche et al., 2008 [7]	30, 37 ($n = 2$)	NR	Substance abuse	NR	Back, then spread		Yes; recurred with repeat cocaine use	9	

Table 2 continued

Author, year	Age and sex	Dose and route	Indication for drug	Initiation of drug to PG onset	Location of lesions	Risk factors for PG	Rechallenge	Naranjo score	Comments
Enoxaparin									
Sobieszczanska et al., 2014 [14]	61 F	80 mg SC	Pulmonary embolism	NR	Abdomen, at injection sites		No	5	
Erythropoietin									
Park et al., 1997 [38]	41 F	NR	End-stage renal failure secondary to diabetic nephropathy	5 days	Right upper arm (injection site), lower back, left thigh, both ankles		No	5	
Etanercept									
Kowalzick et al., 2013 [22]	58 F	50 mg SC weekly	Psoriatic arthritis	5 months	Left temple, vulva, groin		No	7	
G-CSF (mean Naranjo = 4.2)									
Lewerin et al., 1997 [24]	70 M	30 μg/day SC, increased to 75 μg/day after 2 weeks	Myelodysplastic syndrome	18 days	Chin, lip, tongue, behind right ear	Myelodysplastic syndrome	No	3	Recurrence on both arms at 7 months after discontinuation of G-CSF
Miall et al., 2006 [33]	21 F	300 μg/day SC × 5 days	Hodgkin's lymphoma (IIIB)	NR (days)	Chest, arms, left thigh	Hodgkin's lymphoma	No	4	
Ross et al., 1991 [25]	50 F	200 μg/m^2 daily SC × 12 days	Neutropenia secondary to chemotherapy for small cell lung cancer	12 days	Right hand, where eczema had been previously		No	7	
Takagi et al., 1998 [34]	35 M	300 μg/m^2 daily SC × 7 days	Myelodysplastic syndrome	15 days	Left hip	Myelodysplastic syndrome; previous PG 5 years ago, at onset of MDS	No	3	
White et al., 2006 [35]	23 M	NR	Hodgkin's lymphoma (IVB)	NR (days)	Chest, arms, forehead, right thigh, at injection sites	Hodgkin's lymphoma	No	4	

Table 2 continued

Author, year	Age and sex	Dose and route	Indication for drug	Initiation of drug to PG onset	Location of lesions	Risk factors for PG	Rechallenge	Naranjo score	Comments
Gefitinib									
Sagara et al., 2006 [13]	55 M	200 mg/day PO	Adenocarcinoma of lung	2 weeks	Scalp, face, trunk, right thumb, hypogastrium		Yes; gefitinib reintroduced at a reduced dose and PG did not recur	5	
Imatinib									
Pinato and Sharma, 2013 [21]	78 F	400 mg/day PO	Gastrointestinal stromal tumour	1 year	Anterior left leg		Yes; imatinib reintroduced at 300/400 mg on alternate days; PG recurred at same site 8 weeks after stopping corticosteroids	9	
Infliximab									
Jaimes-López et al., 2009 [43]	47 M	5 mg/kg SC q8wks	Ulcerative colitis	6 months	Trunk, abdomen, genitalia, gluteus, limbs, left preauricular region, peristomal area	Ulcerative colitis	Infliximab was continued, despite ulcers	3	
Vandevyvere et al., 2007 [44]	53 F	3 mg/kg SC q8 weeks	Rheumatoid arthritis	6 months	Left foot	Rheumatoid arthritis	No	4	
Vestita et al., 2015 [45]	43 M	NR	Psoriasis	4 years	Posterior aspects of both legs		No	7	PG resolved with minocycline therapy while receiving etanercept for psoriasis
Interferon (mean Naranjo = 5.3)									
Mir-Bonafé et al., 2012 [36]	61 M	18 million units/day SC	Polycythemia vera	5 years	Lateral right and left thighs at injection sites		No	7	
Montoto et al., 1998 [37]	48 F	3–6 million units × 3 days per week SC	Chronic myeloid leukaemia	1 month	Upper left abdomen, at injection sites	Chronic myeloid leukaemia	No	2	
Yurci et al., 2007 [8]	45 F	NR	Hepatitis C	8 weeks	NR		No	7	
Ipilimumab									
Rudolph et al., 2014 [51]	56 F	3 mg/kg IV q3 weeks × 4 doses	Melanoma of rectum	16 weeks	Peristomal		No	6	

Table 2 continued

Author, year	Age and sex	Dose and route	Indication for drug	Initiation of drug to PG onset	Location of lesions	Risk factors for PG	Rechallenge	Naranjo score	Comments
Isotretinoin (mean Naranjo = 6.2)									
Exner et al., 1983 [10]	21 M	1 mg/kg/day PO	Nodulocystic acne vulgaris	6 weeks	Trunk, left thigh		No	7	
Freiman and Brassard, 2006 [26]	38 F	0.5 mg/kg/day PO	Nodulocystic acne vulgaris	1 month	Back		No	7	
Gangaram et al., 1997 [12]	17 M	0.5 mg/kg/day PO	Recalcitrant acne vulgaris	2 weeks	Midline chest		No	7	
Hughes and Cunliffe, 1990 [27]	19 M	1 mg/kg/day PO	Recalcitrant acne vulgaris	3 years	Trunk	Myelodysplastic syndrome	No	3	
Tinoco et al., 2008 [28]	19 M	0.5 mg/kg/day PO	Nodulocystic acne vulgaris	1 month	Pubic, inguinal area, left arm, both legs		No	7	
Lenalidomide									
Dasanu et al., 2015 [11]	81 M	10 mg PO daily, 21 of 28 days	Multiple myeloma	<6 months	Both knees	Multiple myeloma	No	2	
Pazopanib									
Usui et al., 2016 [42]	78 M	800 mg/day PO	Renal cell carcinoma	6 days	Glans penis		No	7	Previously developed sunitinib-induced PG
Propylthiouracil (mean Naranjo = 6.8)									
Boulenger-Vazel et al., 2005 [6]	40 F	NR	Grave's disease	1.5 years	Right ankle		No	7	
Darben et al., 1999 [29]	44 F	NR	Grave's disease	4 years	All four limbs, vertex of scalp, roof of mouth		No	7	
Gungor et al., 2006 [30]	52 F	NR	Grave's disease	2 years	Both lower extremities		No	6	
Hong and Lee, 2004 [31]	27 F	NR	Grave's disease	2 years	Both lower legs, anterior		No	7	
Seo et al., 2010 [32]	60 F	150 mg/day PO	Grave's disease	6 years	Right lateral torso		No	7	

Table 2 continued

Author, year	Age and sex	Dose and route	Indication for drug	Initiation of drug to PG onset	Location of lesions	Risk factors for PG	Rechallenge	Naranjo score	Comments
Red tattoo dye									
Litvinov and Sasseville, 2014 [19]	39 F	Topical	Cosmetic	2 weeks	Left lower leg, at site of tattoo dye application	Crohn's disease	No	3	
Sunitinib (mean Naranjo = 7.4)									
Akanay-Diesel et al., 2011 [16]	69 M	37.5 mg/day PO	Hepatocellular carcinoma	NR	Both lower legs		No	7	
Dean and Zirwas, 2010 [17]	61 F	37.5 mg/day PO	Renal cell carcinoma	1 month	Right distal lateral calf		No	7	
Nadauld et al., 2011 [39]	47 M	50 mg/day PO (4 weeks on/ 2 weeks off)	Renal cell carcinoma (clear cell)	3 months	Right lateral lower leg		No	9	PG transiently improved during 2 weeks off sunitinib
ten Freyhaus et al., 2008 [40]	76 F	25–50 mg/day PO (4 weeks on/2 weeks off)	Gastrointestinal stromal tumour	4 months	Left lower leg, left arm		No	7	
Ueharaguchi et al., 2013 [41]	64 M	50 mg/day PO	Renal cell carcinoma	18 months	Right lower leg		No	7	

bid twice daily, *F* female, *G-CSF* granulocyte colony-stimulating factor, *M* male, *MDS* myelodysplastic syndrome, *NR* not reported, *PG* pyoderma gangrenosum, *PO* by mouth, *SC* subcutaneously, *qxweeks* every *x* weeks, *IIIB* stage III B lymphoma, *IV* intravenously, *IVB* stage IV B lymphoma

drugs indicating probable adverse drug reactions (mean Naranjo score 5–8), i.e. propylthiouracil, isotretinoin, interferon, sunitinib, gefitinib, enoxaparin, erythropoietin, pazopanib, etanercept, ipilimumab, azacitidine, alitretinoin, and ciprofloxacin. Five drugs indicated possible adverse drug reactions (mean Naranjo score 1–4), i.e. G-CSF, infliximab, adalimumab, lenalidomide, and red tattoo dye.

3.1 Isotretinoin

All five patients were being treated for severe acne vulgaris, at a dose of 0.5–1 mg/kg/day [10, 12, 26–28]. In four patients, PG onset was 2–6 weeks after initiation of isotretinoin [10, 12, 26, 28]. In the last patient, PG onset was 3 years later [27], however this patient was later confirmed to have MDS. All five patients presented with lesions on the trunk, and two patients also had limb lesions. All patients experienced ulcer healing with discontinuation of isotretinoin and systemic immunosuppressive therapy (corticosteroids, dapsone, or mycophenolate mofetil). The mean Naranjo score for all cases was 6.2.

3.2 Propylthiouracil

All five reported patients were females being treated for hyperthyroidism [6, 29–32]. Four patients presented with PG on the limbs [6, 29–31] and one presented with PG on the trunk [32]. Lesions appeared between 1.5 and 6 years after propylthiouracil was initiated. In all cases, ulcer healing was observed with discontinuation of propylthiouracil and initiation of systemic corticosteroid therapy. Time to re-epithelialization, reported in four cases, was 2–8 weeks [6, 29–31]. The mean Naranjo score for all cases was 6.8.

3.3 Granulocyte Colony-Stimulating Factor and Other Subcutaneous Injection Medications

Drug-induced PG secondary to G-CSF was reported in five patients [24, 33–35], four of whom had concurrent underlying illnesses that were significant risk factors: MDS ($n = 2$) [24, 34] and Hodgkin's lymphoma ($n = 2$) [33, 35]. The location of lesions was variable between patients and occurred at injection sites in only one patient [35]. In all cases, ulcers gradually improved with discontinuation of G-CSF and systemic corticosteroid therapy. One patient relapsed 7 months after stopping G-CSF and required cyclosporine 600 mg/day for control [24]. The mean Naranjo score for all cases was 4.2.

Interferon was implicated in drug-induced PG in three cases [8, 36, 37], two of which presented with lesions at injection sites [36, 37]. Onset of PG varied from 1 month to 5 years. All three patients experienced wound healing with discontinuation of interferon and initiation of immunosuppressive therapy (corticosteroids, or cyclosporine). The mean Naranjo score for all cases was 5.3.

One patient developed PG at the injection site of enoxaparin (Naranjo = 5) [14], while another patient developed PG at the injection site of erythropoietin (Naranjo = 5) [38].

3.4 Tyrosine Kinase Inhibitors

There were five reports of patients developing PG while taking sunitinib, all of whom were being treated for malignant solid tumours [16, 17, 39–41]. All five patients presented with lesions restricted to the lower limbs. The range of time to onset of PG, reported in four cases, was 1–18 months [17, 39–41]. Two patients were on a dosing regimen of 4 weeks on and 2 weeks off [39, 40]; one of these patients experienced transient improvement in the ulcers during every 2-weeks-off period [39]. Four patients responded well to systemic corticosteroids and discontinuation of sunitinib [16, 17, 39, 41], while in the fifth patient, sunitinib was continued, despite the occurrence of PG [40]. This patient responded to systemic prednisolone initially but relapsed 7 months later. At this time, sunitinib was discontinued and the lesions resolved within 4 weeks. The mean Naranjo score for all cases was 7.4.

Imatinib and gefitinib were reported to be associated with PG in one patient each [13, 21]. In both cases, the tyrosine kinase inhibitor (TKI) was reintroduced at a lower dose. The patient taking imatinib developed recurrence of PG at the same site [21], while the patient taking gefitinib did not develop recurrence [13]. One case of pazopanib-induced PG on the glans penis was reported [42]. This patient had previously developed similar ulcerative lesions diagnosed as PG while taking sunitinib. The mean Naranjo score for non-sunitinib TKIs was 7.0.

3.5 Tumour Necros Factor-α Inhibitors

TNFα inhibitors have been successfully used to treat PG, but we also identified five reports in the literature where these drugs may have been implicated in causing PG [22, 23, 43–45]. Three patients developed PG while taking infliximab [43–45], two of whom had known diseases that predispose to PG—one patient had ulcerative colitis, and the other had rheumatoid arthritis. In the patient with ulcerative colitis, infliximab was continued for disease control and systemic corticosteroids were started [43]. Slow improvement of lesions was observed. In the patient with rheumatoid arthritis, infliximab was stopped [44]. Etanercept was started for disease control and minocycline was added for PG control. Ulcers healed and no relapses

were observed on etanercept therapy. In the last patient, ulcers resolved within 4 weeks of discontinuing infliximab, without additional corticosteroid therapy [45].

One patient developed PG while taking adalimumab for rheumatoid arthritis [39], however lesions did not improve with discontinuation of adalimumab, and improvement was only seen once systemic corticosteroids were initiated. The mean Naranjo score for all cases of TNFα inhibitors was 4.6.

3.6 Cocaine and Levamisole

Thirteen patients in five studies were reported to have developed PG in association with chronic cocaine use [7, 20, 46–48]. Eleven patients presented with limb lesions [20, 46, 47] and one patient developed a Wegener's granulomatosis-like syndrome at the same time as PG [20]. All patients experienced relapse or worsening of PG that was temporally correlated with repeated cocaine use, as confirmed by urine drug testing. Ulcers tended to improve with cocaine abstinence and systemic immunosuppressive therapy (corticosteroids, cyclosporine, cyclophosphamide, infliximab, or mycophenolate mofetil). Three authors strongly suspect the culprit agent to be levamisole rather than cocaine [46–48]. In their geographical locations, a large proportion of cocaine is contaminated with levamisole, although no formal laboratory testing was conducted for confirmation. In their eight cases of cocaine-induced PG, Jeong et al. report serologic findings that are similar to patients with levamisole-associated vasculitis, namely elevated P-ANCA, antimyeloperoxidase antibodies, and antiphospholipid antibodies. The mean Naranjo score among all studies was 9.4.

4 Discussion

Similar to classic PG, cases classified as possible or probable drug-induced PG according to the Naranjo criteria typically began as painful nodules or pustules, which then progress to ulcers over the course of days to weeks. The lesions tend to have boggy, necrotic, sometimes purulent bases, with ragged, undermined borders and surrounding erythema. Histologically, drug-induced PG, like classic PG, presents as neutrophilic infiltration into the dermis, with or without leukocytoclastic vasculitis. The size of the ulcerations is variable, although they may progressively become larger without appropriate treatment. Once healed, permanent cribriform scarring often remains.

Pathergy (characterized by the development of PG at the site of trauma) has been reported in 20–30% of patients with PG. In cases where PG lesions develop after the injection, pathergy is suspected to play a role.

The age and sex distribution of patients who develop drug-induced PG is comparable with the age and sex distribution of patients receiving the suspected drugs (i.e. females taking propylthiouracil for Grave's disease, and young adult males taking isotretinoin for acne vulgaris) (Table 2). Based on the sample size available, there appears to be no demographic risk for drug-induced PG.

Eleven patients (22%) in our sample had a concurrent underlying disease that predisposed them to developing PG: MDS ($n = 4$), haematologic malignancy ($n = 4$), rheumatoid arthritis ($n = 2$), or IBD ($n = 1$). This is appreciably lower than the reported incidence of 50% of all PG patients having underlying disease [1, 4]. This difference suggests that the use of drugs discussed in this paper is a risk factor for PG.

The strongest evidence for drug-induced PG concerns cocaine and levamisole. Because patients often continued cocaine use after the onset of PG, we have evidence of temporal correlation between cocaine use and relapse or worsening of ulcers. The Naranjo scores for these cases are 9 or 10, suggesting that the occurrence of PG is definitely linked to cocaine use. Therefore, if PG is suspected, it is important to ascertain cocaine use in the patient's history. Because levamisole is known to cause other immune-mediated reactions, such as vasculitis, there is a clinical suspicion of levamisole being the cause of PG in these cases; however, no laboratory testing was performed to confirm the presence of serum or urine levamisole in these patients.

Three drugs, i.e. propylthiouracil ($n = 5$), isotretinoin ($n = 5$), and sunitinib ($n = 5$), demonstrated consistently high (5 or greater) Naranjo scores in multiple case reports, suggesting that for these drugs, PG was a probable adverse drug reaction.

TNFα inhibitors have been shown to effectively treat refractory PG; however, there were five reports of this class of drugs causing PG. All five of these patients had systemic inflammatory disease, for which TNFα inhibitors were indicated. Therefore, it is suspected that these drugs did not in fact cause PG, but rather failed to suppress it [23]. Alternatively, these may represent paradoxical reactions due to a shift towards T helper-17 polarization.

Drug-induced PG is frequently initially misdiagnosed as bacterial infection. Although wounds may become secondarily infected, systemic antibiotics provide little to no relief. As is the case with all severe adverse drug reactions, the mainstay of therapy is discontinuation of the suspected drug. Systemic corticosteroids and immunosuppressive agents can accelerate healing time but are not curative if the causative drug is continued.

Ultimately, drug-induced PG poses a diagnostic challenge. Due to the severity of the reaction, giving placebo or rechallenging the drug is usually unacceptable. Therefore, correlation between drug administration and PG may be difficult to establish.

4.1 Limitations

Drug-induced PG is a very rare adverse event with no standard for diagnosis. Therefore, it is possible that some of these cases were misdiagnosed and were not in fact drug-induced PG. This is particularly an issue in the case of cocaine as some cases may present similar to, or concurrently with, Wegener's granulomatosis [20].

5 Conclusions

Drug-induced PG is a rare but serious adverse drug reaction. Drugs should be considered as a possible triggering event whenever PG is suspected or diagnosed. Where there is clinical suspicion of this reaction, the suspected drug should be discontinued immediately. It is important to recognize that the onset of PG can be years after a therapy is started and that there is no specific clinical or pathological pattern that suggests drug-induced PG. Clinicians should particularly consider drug causes for PG in patients taking propylthiouracil, isotretinoin, or sunitinib, and in patients with a history of cocaine use.

Compliance with Ethical Standards

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