

Concurrent pyoderma gangrenosum and Takayasu arteritis in an infant: diagnostic challenges and treatment considerations

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ABSTRACT

Background. Takayasu arteritis (TA) is an uncommon chronic inflammatory and autoimmune disease primarily affecting large vessels, particularly the aorta and its branches. Skin manifestations have been documented in association with TA. Pyoderma gangrenosum (PG) is a chronic neutrophilic dermatosis characterized by destructive, necrotizing, and painful ulcers, predominantly found on the lower extremities. The coexistence of PG and TA is extremely rare, with most reported cases involving adult patients. Interestingly, the association between PG and TA appears to be more common in Japan compared to North American and European populations. Childhood TA (c-TA) accompanied by PG is exceptionally rare, with only 10 cases reported in the literature thus far.

Case Report. We present the case of a 7-month-old patient initially diagnosed with PG. Despite aggressive immunosuppressive therapy, the patient's high acute phase reactants remained elevated. Although the abdominal ultrasound was normal, advanced imaging was performed due to severe abdominal pain. Contrast-enhanced computerized tomography angiography of the aorta and its branches revealed extensive vascular involvement consistent with TA.

Conclusion. In this report, we highlight an infantile case of PG that was subsequently diagnosed as infantile TA. Recognizing the rare association between PG and TA is important. Thorough evaluation and prompt diagnosis of TA in infants with PG can guide further investigations and prevent vascular complications.

Key words: Takayasu arteritis, pyoderma gangrenosum, vasculitis.

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis. It is characterized by destructive, necrotizing, and noninfectious ulceration of the skin and is most often located on the lower extremities. A total of 18 patients with PG-related Takayasu Arteritis (TA) have been reported in the literature, and its association with childhood Takayasu Arteritis (c-TA) has been reported in only 10 cases.^{1,2}

TA is a rare form of vasculitis involving large vessels. It is a chronic, autoimmune, granulomatous, and inflammatory disease that

can cause dilatation, occlusion, stenosis and/or aneurysm by affecting the aorta and its main branches. Only approximately 30% of all cases are children. In the early stages of the disease, fever, loss of appetite, night sweats, joint pain and rash are observed, while signs of vascular insufficiency are observed in the late stages.¹

The incidence of TA and PG shows racial differences. The highest incidence rate is in Japan, while it is rare in North America and Europe.^{3,4}

Herein, we present a case of infantile PG that was later diagnosed as infantile TA and review the literature.

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Case presentation

A 7-month-old girl was admitted to the pediatric rheumatology inpatient clinic for skin lesions that had been present since she was 3 months old. She had papulopustular skin lesions, some of which were large necrotic ulcers, in many parts of the body. The lesions were mostly located on the upper and lower extremities and the gluteal region as indicated in Fig. 1 and 2. Apart from extensive skin lesions, her physical examination was normal with normal vital signs. Acute phase reactants were elevated (erythrocyte sedimentation rate [ESR]: 100 mm/hr, C-reactive protein [CRP]: 225 mg/L). Complete blood count and blood biochemistry were normal. In the etiological evaluation, investigations were conducted for immunodeficiency, infectious, autoinflammatory, autoimmune rheumatological diseases, and malignancy. Therefore, the following tests were performed: serum immunoglobulins, immunoglobulin subclasses, lymphocyte subtypes, nitroblue tetrazolium test, and tests for leukocyte adhesion deficiency, all of which yielded normal results. Blood and skin swab cultures were also negative. Additionally, bone marrow examination and imaging studies were performed to rule out a paraneoplastic reaction,

and they were normal. An autoinflammatory disease gene panel (17 genes, including the *PSTPIP1* gene) was studied. Upper and lower gastrointestinal endoscopies were normal, excluding inflammatory bowel disease (IBD). Abdominal USG, echocardiography, and blood pressure were normal.

A skin biopsy was performed. Hyperkeratosis on the surface, thinning of the epidermis, scar tissue in the dermis, mixed-type inflammation, vascular proliferation, and necrosis were observed. IgM, IgG, and C3 accumulation were not observed. Elastic fiber loss was noted in the scar tissue with elastic Van Geisen stain. Ki-67 was positive in the epithelial basement. Multiple bacterial cultures from pustules and abscesses showed no evidence of bacterial infection. It was stated that these findings were consistent with the late period of PG.

The patient was ultimately diagnosed with idiopathic PG, and treatment was initiated with intravenous immunoglobulin (IVIG) at a dose of 1 g/kg, along with high-dose pulse methylprednisolone administered at a dose of 30 mg/kg/dose for a duration of 3 days. Despite the administration of conventional treatment, the patient did not experience regression of new



Fig. 1. Pyoderma gangrenosum lesion with necrotizing vasculitis and hyperkeratosis over the triceps muscle of the left arm.



Fig. 2. Pyoderma gangrenosum lesion with necrotizing vasculitis and hyperkeratosis over the medial malleolus of the right ankle.

lesions or signs of inflammation. In light of the suspicion of an underlying autoinflammatory disease, anakinra was introduced as part of the treatment plan. The initial dose of anakinra was started, and it was gradually increased up to 8 mg/kg/day to achieve an optimal therapeutic effect.

Considering the patient's persistent symptoms and the absence of a detected mutation in a specific gene associated with autoinflammatory diseases, the decision to transition from anakinra to tocilizumab is a reasonable approach. In addition to daily steroid treatment, tocilizumab was initiated to target the underlying inflammatory process. Tocilizumab is expected to provide a different mechanism of action and potentially better control of the patient's symptoms.

After two months of treatment with tocilizumab, the patient experienced regression of old lesions, and no new lesions appeared. However, in the third month, severe PG lesions recurred. To address this, the decision was made to initiate infliximab treatment at a dose of 5 mg/kg every 4 weeks. This intervention resulted in the resolution of PG lesions and the normalization of acute phase reactants, providing positive outcomes for the patient for the first time.

At the age of 2.5 years, the patient, who had been receiving infliximab treatment for one year without developing new lesions, was admitted to the hospital with fever. On examination, it was noted that new PG lesions had recurred. Additionally, laboratory tests revealed elevated acute phase reactants, with an ESR of 90 mm/h and CRP level of 189 mg/L. Furthermore, thrombocytosis was observed, with a platelet count of 1,143,000/mm³. These findings suggest a flare-up of the patient's PG and indicate ongoing inflammatory activity. Further evaluation and adjustment of the treatment approach may be necessary to effectively manage the condition and control the symptoms.

Despite the absence of diarrhea episodes or bloody stools, the patient was re-evaluated for IBD due to the association between PG and occult IBD. Fecal calprotectin, a marker of

intestinal inflammation, was slightly elevated at 96 µg/g (normal <80). To further assess intestinal involvement, magnetic resonance (MR) enteroclysis was performed, which reported normal findings.

During the evaluation for vasculitides associated with the patient's condition, thoracoabdominal computed tomography angiography (CTA) revealed several findings. There was evidence of vasculitis and aneurysmal dilatation in the ascending aorta and its main branches. Specifically, concentric wall thickening, reaching a thickness of 3.5 mm, was observed in a segment of approximately 5 cm length at the suprarenal level of the aorta as shown in Fig. 3. This suggests active inflammation and structural abnormalities in that region. Furthermore, slight luminal narrowing was observed in a segment approximately 7 mm long at the origin of the superior mesenteric artery, which may impede blood flow to the intestine as shown in Fig. 3. Color Doppler ultrasonography revealed additional findings related to the patient's arterial system. Thickening of the arterial walls

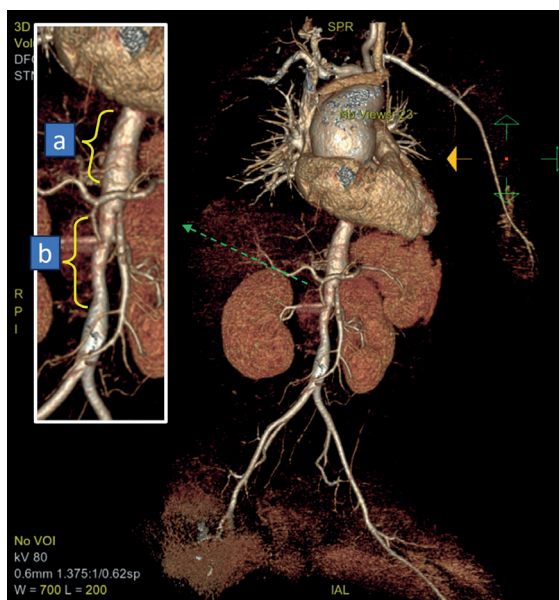


Fig. 3. Thoracoabdominal vascular mapping through computerized tomography angiography.

a. Aneurysmal dilatation at the suprarenal level of the aorta. **b.** Narrowing at the origin of the superior mesenteric artery along the abdominal aorta.

of the common carotid arteries was observed, indicating involvement of these arteries in the vasculitic process. Additionally, there were narrowing of the lumen, suggesting reduced blood flow through the affected carotid arteries.

According to the American College of Rheumatology (ACR) 1990 criteria⁵ and the European League Against Rheumatism/Pediatric Rheumatology International Trials Organization/Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) criteria⁶, the vascular findings observed in the patient are consistent with the diagnosis of c-TA. Considering this diagnosis, the patient was started on cyclophosphamide treatment at a dosage of 500 mg/m² monthly. The patient has received three infusions of cyclophosphamide thus far. It is encouraging to note that treatment with cyclophosphamide resulted in the normalization of acute phase reactants, indicating a reduction in the inflammatory response. Additionally, there were no new occurrences of PG lesions, suggesting a positive response to the treatment in terms of disease activity.

Discussion

The association between TA and PG-like vasculitic lesions is indeed rare. The first description of this association was reported in 1966.³ The coexistence of these two conditions poses diagnostic and therapeutic challenges, as the management of TA and PG requires different treatment approaches.

When conducting a literature search, we found that there have been reports of 18 cases, including adults, with the coexistence of TA and PG-like vasculitic lesions.^{1,4,7-10} Among these cases, only 10 were reported in children. In rare cases, TA has been reported to coexist with other conditions, such as ulcerative colitis, Crohn's disease, rheumatoid arthritis, and autoimmune hemolytic anemia.¹¹ These associations highlight the complex nature of autoimmune and inflammatory diseases

and the potential overlap between different conditions. Further research is needed to understand the underlying mechanisms and the clinical management of these rare coexisting conditions.

Studies have provided support for the notion that PG-like vasculitic lesions can serve as the initial skin manifestation of TA. In our patient, at the time of the initial diagnosis of PG, there were no evident clinical or laboratory findings suggestive of TA. It is important to note that the association of PG-like vasculitic lesions with TA has been reported in only a few cases, highlighting its rare occurrence.^{1,4,7-9}

In the adult population, the average age of diagnosis for PG is approximately 22.5 years, while for TA, it is approximately 26.0 years.¹ During our literature review, we identified 10 cases of concurrent TA and PG, as listed in Table I. The median age at onset was 10 years for PG and 9 years for TA, with a male predominance observed (M/F ratio of 3/2). Notably, PG and TA can manifest at any stage of the disease process. In 50% of the cases (5 out of 10), PG was diagnosed an average of 5 years earlier (ranging from 1.5 to 9 years) than c-TA. In 40% of the cases (4 out of 10), PG and c-TA were diagnosed simultaneously, and in 1 case, PG was diagnosed within 2 years after the c-TA diagnosis.²

In the case of our patient, TA was diagnosed 21 months after the initial diagnosis of PG, which is within the range reported in the literature. This highlights the variable temporal relationship between the two conditions and the importance of considering TA in the diagnostic workup of patients with PG, even if there is a considerable time gap between the two diagnoses.

Based on the available literature, information regarding the prediction of c-TA development in patients with PG-like vasculitic lesions is limited. Among the 10 reported patients, common findings associated with c-TA were observed in the following order of frequency: fever (70% or 7/10), bruises (60% or 6/10),

Table I. Review of cases with Takayasu arteritis and pyoderma gangrenosum.

Authors, years & reference	Sex	Age at onset of the systemic manifestation	Age at onset of the PG manifestation	Age at onset of the c-TA manifestation	Systemic symptoms	Vascular involvement; location	PG lesion location and histopathologic manifestations	Laboratory tests
Shen et al. 2022 ²	Case 1 M	6	6	7,5	Fever and chest pain	Aneurysms of AAO, AOA and its branches, DAO, and AA	Neutrophilic infiltration and necrotizing vasculitis	Elevated WBC, ESR, and CRP
	Case 2 M	5	5	5	Fever and harsh systolic murmurs over the bilateral CA	BCT and bilateral ICA were narrowed with local dilatation; AOA, the proximal end of the BCT, CCA, VA, SBC, and AA were thickened, stenosis of the SMA	Neutrophils and lymphocyte infiltration in vessel walls and vasculitis	Elevated WBC, ESR, and CRP
	Case 3 M	10	10	10	Fever, cough, wheezing, shortness of breath, and chest pain	Thickening of the bilateral CCA and SMA	Infiltration of neutrophils and lymphocytes and vasculitis	Elevated WBC, ESR, and CRP
Zhang et al. 2019 ¹	F	N/A	17	24	Left arm weakness, dizziness, discrepancy in systolic BP, spray-like noise on the left SBC and bilateral FA	The left CA was narrowed and blocked; the left SBC, FA, SFA, and left POA were thickened; the AAO, AOA, DAO, and AA were thickened; the CT and SMA were occluded; and stenosis in the lumen of the HA and SA	A large number of neutrophils, plasma cells, lymphocytes, and multinucleated giant cells had infiltrated the dermis and subcutaneous tissue; no vasculitis described	Elevated ESR and CRP
Vettiyil et al. 2017 ¹⁰	F	8	10	8	Pain and claudication in the legs and back; an absence of pulses in the carotid, brachial, radial, popliteal, and dorsalis pedis on the left side and right femoral, popliteal, and dorsalis pedis; right-sided carotid bruits	Dilation of the AAO and narrowing of the left CCA; the bilateral SBC and AXA were narrowed at the origin and proximal portion	Suggestive of PG; the presence of vasculitis was not described	Elevated ESR and CRP
Barrera-Vargas et al. 2015 ⁴	M	25	17	26	Fever, chest pain, cough, dyspnea, lightheadedness and syncope, discrepancy in systolic BP, diminished pulses and bruits over the left CA	AO dilatation, narrowing and wall thickening of the left CCA, and CT stenosis, as well as thickening at the origin of the SMA and left ReA	No skin biopsy record	Elevated ESR and CRP

AA, abdominal aorta; AAO, ascending aorta; AO, aorta; AOA, aortic arch; AXA, axillary artery; BCT, brachiocephalic trunk; BP, blood pressure; CA, carotid artery; CCA, common carotid artery; CRP, C-reactive protein; CT, celiac trunk; DAO, descending aorta; ESR, erythrocyte sedimentation rate; F, female; FA, femoral arteries; HA, hepatic artery; ICA, internal carotid artery; M, male; NA, not available; PG, pyoderma gangrenosum; POA, popliteal artery; ReA, renal artery; SA, splenic artery; SBC, subclavian artery; SFA, superficial artery; SMA, superior mesenteric artery; ThA, thoracic aorta, WBC: white blood cells.

Table I. Continued.

Authors, years & reference	Sex	Age at onset of the systemic manifestation	Age at onset of the PG manifestation	Age at onset of the c-TA manifestation	Systemic symptoms	Vascular involvement; location	PG lesion location and histopathologic manifestations	Laboratory tests
Minagawa et al. 2009 ⁴	F	21	16	21	Low-grade fever, discrepancy in systolic BP, dysesthesia in the arms, fatigue, diminished left radial pulse and carotid bruits	Stenosis and thickened walls in the SBC, left carotid and right ReA	Necrotizing vasculitis with lobular panniculitis in the deep dermis	No record
Ghosn et al. 2008 ¹⁵	F	7	7	7	Acute onset right wrist drop	Marked aneurysmal dilatation of the AAO; significant enlargement of the BCT, right CCA, and right AXA; occlusion of left and right SBC and collateral vessel formation	Epidermal necrosis and ulceration, Elevated ESR	Elevated ESR
Dagan et al. 1995 ¹⁶	M	4	0,75	4	Restlessness, fatigue, fever, heart murmurs, an absence of both radial pulses	Severe aneurysmatic dilation of the AAO, severe stenosis of the left radial AAO	Granulomatous dermatitis and panniculitis, with no evidence of vasculitis	Elevated ESR
Perniciaro et al. 1987 ¹¹	M	17,5	19	19	Intermittent fever, multiple vascular bruits	NA	Necrotizing vasculitis with polymorphonuclear leukocytes and fibrinoid changes in vessel walls	Elevated ESR
Present case	F	3	0,58	3	Fever and abdominal pain	Aneurysmal dilatation of the AAO; Diffuse concentric wall thickening in the ThA and AA; slight luminal narrowing at the origin of the SMA	Hyperkeratosis, mixed-type inflammation, vascular proliferation, and necrosis. Elastic fiber loss in the scar tissue with elastic Van Geisen stain. Positive KI-67 in the epithelial basement.	Elevated ESR and CRP

AA, abdominal aorta; AAO, ascending aorta; AO, aorta; AOA, aortic arch; AXA, axillary artery; BCT, brachiocephalic trunk; BP, blood pressure; CA, carotid artery; CCA, common carotid artery; CRP, C-reactive protein; CT, celiac trunk; DAO, descending aorta; ESR, erythrocyte sedimentation rate; F, female; FA, femoral arteries; HA, hepatic artery; ICA, internal carotid artery; M, male; NA, not available; PG, pyoderma gangrenosum; POA, popliteal artery; ReA, renal artery; SA, splenic artery; SBC, subclavian artery; SFA, superficial artery; SMA, superior mesenteric artery; ThA, thoracic aorta, WBC: white blood cells.

and pulselessness (40% or 4/10). In terms of laboratory findings, an elevated ESR was observed in 90% of cases, while CRP elevation was observed in 70% of cases. Skin biopsy was performed in almost all patients (90%), with vasculitis being observed in 55.6% (5/9) of the patients, not detected in 22.2% (2/9), and with no available records in 22.2% (2/9) of cases. The most commonly involved vessels were the aorta and its branches (7/9), followed by the common carotid arteries (66.7% or 6/9), subclavian arteries (6/9), mesenteric arteries (44.4% or 4/9), and abdominal aorta (3/9). It is important to note that these findings are based on a small number of reported cases, and further research is needed to better understand the characteristics and predictive factors of c-TA in patients with PG-like vasculitic lesions.

Various hypotheses have been proposed to explain the association between PG and TA. One hypothesis is that both diseases involve an increase in proinflammatory cytokines, such as interleukin (IL)-6, IL-8, IL-18, IL-23, and tumor necrosis factor- α (TNF- α). These cytokines have been found to be elevated in both the TA and PG, suggesting similar underlying mechanisms in the two conditions.^{1,2} Establishing a temporal connection between PG and TA can be challenging due to the lack of specific immunoglobulin markers and the delayed onset of vascular symptoms in TA. Additionally, the nonspecific findings during the early "prepulseless" stage of TA may not be noticeable, especially if PG does not show signs at the time of diagnosis. There are also hypotheses that suggest the treatment of PG may delay the onset of TA symptoms.^{2,12} Ujiie et al.¹³ reported that PG associated with TA tends to have more extensive skin involvement than PG without TA.

In our case, the patient presented with extensive papulopustular lesions, including some necrotic ulcerated lesions, predominantly on the upper extremities, ankle, gluteal region, and lower extremities. The distribution of lesions in the lower extremities aligns with the

findings reported in the literature.⁵ It is worth noting that the presence of skin involvement in patients with TA does not necessarily indicate a worse prognosis for the disease.¹⁰

The extent and distribution of skin involvement can vary among individuals with TA, and it is important to evaluate and monitor the patient's overall clinical presentation, including systemic symptoms and vascular involvement, to determine the appropriate management and treatment approach.¹⁴

Based on the information obtained from the literature and the case we presented, it is important to raise suspicion and consider the possibility of an underlying diagnosis of TA in cases of PG with unclear etiology, particularly in young female patients. The association between PG and TA, although rare, has been reported in the literature, and recognizing this potential association can guide further investigations and appropriate management.¹⁵ When encountering a patient with PG, especially in an infantile age group, thorough evaluation and investigation should be conducted to identify any underlying systemic conditions, including vasculitis such as TA. Prompt recognition and diagnosis of TA in such cases are crucial for initiating appropriate treatment and preventing potential complications associated with vascular involvement.

Ethical approval

Informed consent was obtained from the parents of the child.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: GÖB, BS; data collection: GÖB; analysis and interpretation of results: GÖB, BS; draft manuscript preparation: GÖB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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