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A Severe Necrotic Intertriginous Eruption in a Patient on Pembrolizumab for Advanced Melanoma

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Abstract

A 62-year-old woman with hypertension, hypercholesterolaemia, increased body mass index and pre-existing hidradenitis suppurativa (HS) developed unresectable locally advanced melanoma and commenced pembrolizumab 400mg intravenously every six weeks.

Eight months after commencing pembrolizumab, she developed progressive skin breakdown affecting the suprapubic and groin creases bilaterally. There were no nodules or abscesses suggestive of active HS. The eruption was initially diagnosed as chronic intertrigo and treated with topical clotrimazole. On subsequent dermatology review, she had extensive erythema and superficial erosion affecting all intertriginous areas alongside hypopigmented wrinkled areas of skin. Differential diagnoses from the treating dermatology consultant included pembrolizumab-associated vitiligo and extragenital lichen sclerosus; the presentation was not consistent with HS. A punch biopsy was recommended but initially declined because of significant surgical anxiety.

The eruption continued to deteriorate, resulting in hospital admission with severe pain, fatigue and profound functional impairment. Examination on hospital admission demonstrated widespread erosive, inflammatory, hypopigmented and atrophic changes involving multiple intertriginous sites.

Punch biopsy during hospital admission revealed almost complete epidermal necrosis with a prominent neutrophilic infiltrate, without features of lichen sclerosus or immunobullous disease; histopathological findings were not consistent with her pre-existing diagnosis of HS. Skin swabs grew a heavy growth of Staphylococcus aureus consistent with superimposed bacterial infection.

A severe pembrolizumab-associated immune-mediated cutaneous toxicity with superimposed bacterial infection was considered the likely diagnosis based on clinical features, serology, microbiology and histopathology. The toxicity was graded as 3-4 according to the Common Terminology Criteria for Adverse Events (CTCAE) by the treating medical oncology consultant. Pembrolizumab was discontinued and intravenous methylprednisolone 2mg/kg was initiated, followed by a slow oral prednisolone taper. She received a short course of oral antibiotics for superadded bacterial infection and intensive wound care. The eruption improved significantly after the start of intravenous steroids, although she required a month-long hospital admission with ongoing community nursing and rehabilitation following discharge.

Categories: Therapeutics, Oncology, Dermatology
Keywords: advanced melanoma, cancer immunotherapy, cutaneous immune-related adverse events, pembrolizumab side effect, pembrolizumab toxicity

Introduction

Pembrolizumab is an anti-PD-1 immune checkpoint inhibitor that was approved in the UK by the National Institute for Health and Care Excellence (NICE) as a first-line treatment option for advanced (unresectable or metastatic) melanoma in November 2015 [1].

In the age before immunotherapies and targeted treatments, the five-year survival rate for metastatic melanoma was <5% with a median survival rate of 6-9 months [2]. The introduction of immune checkpoint inhibitors has substantially altered this prognosis; a 10-year follow-up for the phase 3 KEYNOTE-006 has demonstrated the durability of pembrolizumab in advanced melanoma, with approximately one third of patients remaining alive at 10 years (at 10 years, overall survival was 34% with pembrolizumab compared with 23.6% with ipilimumab). These data demonstrate that a proportion of patients can achieve prolonged disease control following treatment with PD-1 blockade, including after completion of a finite treatment course [3].

Despite the survival benefit associated with immune checkpoint inhibitors, treatment can result in a broad spectrum of immune-related adverse events (irAEs) affecting virtually any organ system and commonly

affecting the skin [4].

Cutaneous manifestations are among the most frequently reported irAEs, affecting up to 60% of immune checkpoint inhibitor-treated patients. The clinical presentations encompass maculopapular, eczematous, psoriasiform and lichenoid eruptions, pruritus, vitiligo and, less commonly, immunobullous disorders and severe cutaneous adverse reactions. The onset of cutaneous irAEs is variable and often phenotype-dependent: Maculopapular eruptions and pruritus typically develop within the first few weeks of treatment, whereas immunobullous reactions on vitiligo may present several months after treatment initiation. Importantly, certain cutaneous toxicities may persist or present following treatment discontinuation.

Consequently, a high index of suspicion is required when assessing new or atypical dermatological presentations in patients receiving, or with a history of exposure to immune checkpoint inhibitors. Particular attention should be paid to severe skin pain, blistering, erosions, epidermal detachment, mucosal involvement, facial oedema and systemic symptoms, which may indicate significant cutaneous toxicity and warrant urgent dermatological assessment [5].

Intertriginous and inverse eruptions related to checkpoint inhibitors are more rarely reported but are becoming increasingly recognised. Totonchy et al. described an inverse psoriasiform eruption in a patient receiving pembrolizumab for metastatic melanoma, affecting the inguinal and intergluteal folds [6]. Similarly, Sethi et al. reported two cases of PD-1 inhibitor-associated inverse lichenoid eruptions [7]. A retrospective study of immune checkpoint inhibitor-associated psoriasiform eruptions also identified an inverse phenotype in 13 patients, most commonly affecting the inguinal folds [8]. These reports highlight the potential for immune checkpoint inhibitors to cause atypical flexural eruptions that may mimic infection.

Our case describes a severe erosive and necrotic intertriginous eruption in a patient receiving pembrolizumab. Although similar flexural eruptions have previously been reported, the extent of epidermal necrosis and tissue damage in this case was unusual. The clinical presentation and histopathological findings may suggest a potentially severe manifestation of pembrolizumab-associated cutaneous toxicity, highlighting the importance of recognising atypical presentations that may initially mimic infection.

Case Presentation

Before pembrolizumab initiation: melanoma diagnosis and staging

A 62-year-old woman with a past medical history of hypertension, hypercholesterolaemia, raised body mass index and hidradenitis suppurativa (HS) (managed only with topical anti-bacterial treatments) presented with an atypical pigmented lesion on her left upper arm. It had rapidly increased in size, with recurrent bleeding. On examination, she had Fitzpatrick type II skin and the index lesion measured 15mm by 15mm with deep brown/purple pigment under dermoscopy. It raised suspicion for melanoma skin cancer. Urgent excision was performed.

Histology revealed invasive nodular malignant melanoma with a Breslow thickness of 4.7mm. There was ulceration, but no lymphatic, blood vessel or perineural invasion, no microsatellites and a mitotic rate of 11 per mm^2. Excision margins (invasive) were 4mm peripherally and 6mm deep. It was summarised as a PT4B melanoma of the left upper arm.

Molecular analysis revealed no variants of clinical significance in BRAF or KIT. Initial CT staging of the head, neck, thorax/abdomen/pelvis showed no evidence of distant metastatic disease.

She was referred for wide local excision of the lesion and declined sentinel lymph node biopsy at that time due to significant surgical anxiety. Further staging scans showed an enlarged left axillary lymph node. Core needle biopsy of the node was performed, and histology confirmed metastatic melanoma. According to the American Joint Committee on Cancer (AJCC) staging system [9], the melanoma was classified as stage 3C (PT4b cN1b cM0) comprising an ulcerated primary tumour greater than 4mm in thickness and one clinically detected, biopsy-confirmed regional axillary lymph node metastasis, with no evidence of distant metastatic disease. The patient declined left axillary dissection with curative intent. Later CT scans revealed a progressive left axillary tumour deposit that had become unresectable (see Figure *1*).

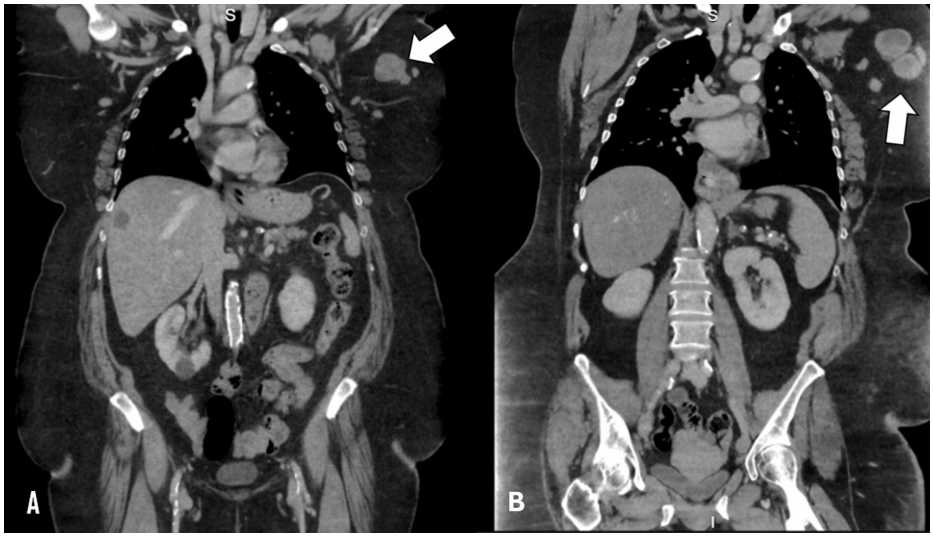


FIGURE 1: A: CT staging scan prior to the start of pembrolizumab showing left axillary lymphadenopathy. B: CT staging scan 10 months after the start of pembrolizumab showing progressive left axillary lymphadenopathy, as well as subcutaneous fat stranding and cutaneous thickening in the lower abdomen and groin area

Pembrolizumab initiation (month 0)

Having declined immunotherapy earlier on in her treatment, in the absence of surgical options, the patient agreed to commence on single-agent pembrolizumab for unresectable locally advanced disease at a dose of 400mg intravenously every six weeks.

Intertriginous eruption first noted at oncology appointment (month 8)

Eight months after starting pembrolizumab, she began to experience a breakdown of skin in the suprapubic crease and groin bilaterally. Her General Practitioner had prescribed her one week of oral flucloxacillin with no improvement in her rash, skin swabs taken at this appointment subsequently came back negative. A week later, examination findings in oncology were thought to be consistent with chronic intertrigo. At this appointment, she was prescribed clotrimazole cream to be used once daily for two weeks, a combination of lymecycline 408mg once daily for 28 days, and daily topical antibacterial washes for a potential flare of HS and referred to dermatology. Immunotherapy was deferred for four weeks in total during her wait for dermatology review but then re-started. Figure *2* shows an area of the rash at this oncology appointment.

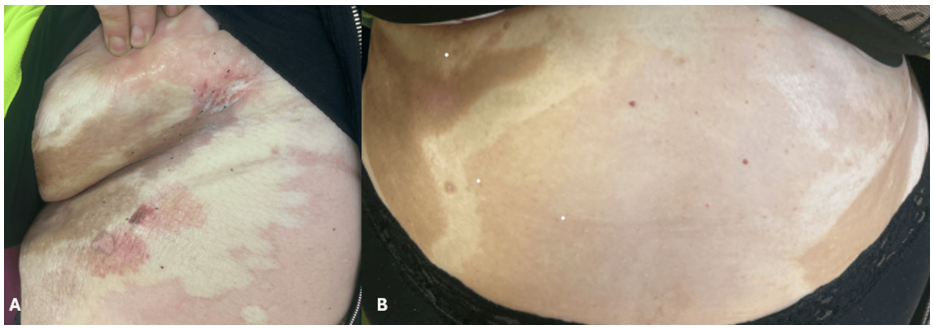


FIGURE 2: A: Left groin; B: abdomen eight months after starting pembrolizumab; images show evidence of hypopigmented patches as well as the beginning of erosion in the left groin

Worsening intertriginous eruption at dermatology review (month 9)

On review by dermatology a month later, the rash had progressed to large patches of erythema with superficial erosion affecting the suprapubic/groin folds and sub mammary area. In addition, she had

multiple patches of pale wrinkly skin affecting her axillae. The impression was pembrolizumab-induced vitiligo on her abdomen and possible extragenital lichen sclerosus affecting the intertriginous areas. She was commenced on daily antibacterial washes, once daily Trimovate ointment, daily silicone dressings to affected areas and analgesia. She was referred for a skin biopsy. Figure *3* shows the rash at the point of dermatology review.



FIGURE 3: Photos taken at the dermatology appointment. A: Progressive erosion in the groin. B: Submammary area erosions. C: Axillary skin changes raised suspicion of extra genital lichen sclerosus

Admission to hospital and investigations (month 10)

The rash continued to worsen at home and she was admitted to hospital due to immobility and fatigue. She had widespread erosive inflammatory hypopigmented atrophic skin changes in intertriginous areas as seen in Figure *4*. She had no mucosal involvement, her observations were normal and she was afebrile. The involved body surface area was not recorded but the toxicity was graded as 3-4 according to the Common Terminology Criteria for Adverse Events (CTCAE) by the treating medical oncology consultant. This grading was given due to the extensive painful erosions and significant functional impairment limiting self-care and activities of daily living. Initial investigations are shown in Table *1*. Histopathology images from punch biopsy taken on hospital admission are shown in Figure *5*.

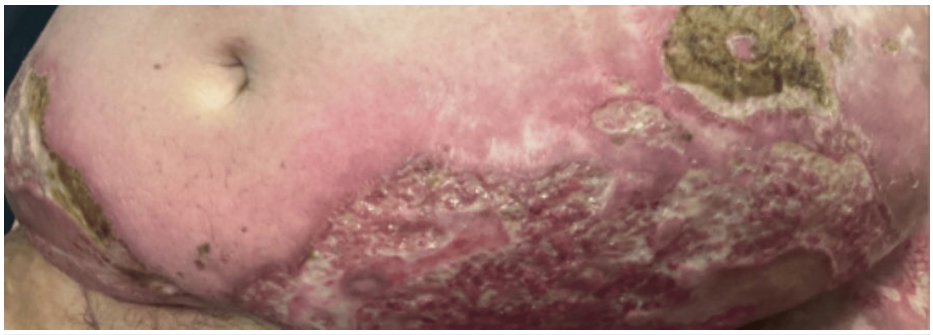


FIGURE 4: Groin areas showing widespread erosion at hospital admission, 10 months after the start of pembrolizumab

Clinical Assessment and Laboratory Findings	
Observations	**A**: Own; **B**: RR 18/min, Sats 95% on room air, good air entry in both lung bases;**C**: HR 87, BP 140/70; **D**: GCS15/15, Temperature 37.1; **E**: Abdomen soft, non-tender, extensive ulcerating lesions over the whole lower abdomen with crusting-no spreading erythema or warmth.
Serology	Hb 91, WBC 11, Neutrophils 8.97, Lymphocytes 1.01, Platelets 483, ALT 48, ALP 133, Albumin 32, Creatinine 45, Urea 7.9, eGFR >90, CRP 155. **Venous blood gas**: **normal**, including lactate
Skin swabs	**Left groin erosion**: Skin flora only; **right groin erosion**: Mixed colonising flora; **abdomen erosion**: heavy growth of Staphylococcus Aureus sensitive to penicillins
Punch biopsies taken from the right submammary area (see Figure 5 for histopathological images: A) for histology; B) for immunofluorescence)	**A**) The surface epithelium within this specimen is almost entirely necrotic and replaced by large numbers of inflammatory cells. There is a small amount of viable epithelium, and this is covered with necrotic keratin. There is no homogenisation to suggest lichen sclerosus. No actual bulla is seen. **B**) Immunofluorescence is negative for IgG, IgA, IgM and C3. **Conclusion**: This is certainly a very severe necrotic rash. The large numbers of neutrophils in the surface layers might suggest an immunotoxicity rash. No evidence of a bullous disorder.

TABLE 1: Initial hospital clinical assessment and investigation results

Reference ranges: Hb: 120–160 g/L; WBC: 3.6–11.0 × 10^9/L; Platelets: 150–400 × 10^9/L; ALT: 0–33 IU/L; ALP: 30–130 IU/L; Albumin: 35–50 g/L; Creatinine: 45–84 µmol/L; Urea: 2.5–7.8 mmol/L; eGFR: >59 mL/min/1.73 m^2; CRP: ≤5 mg/L

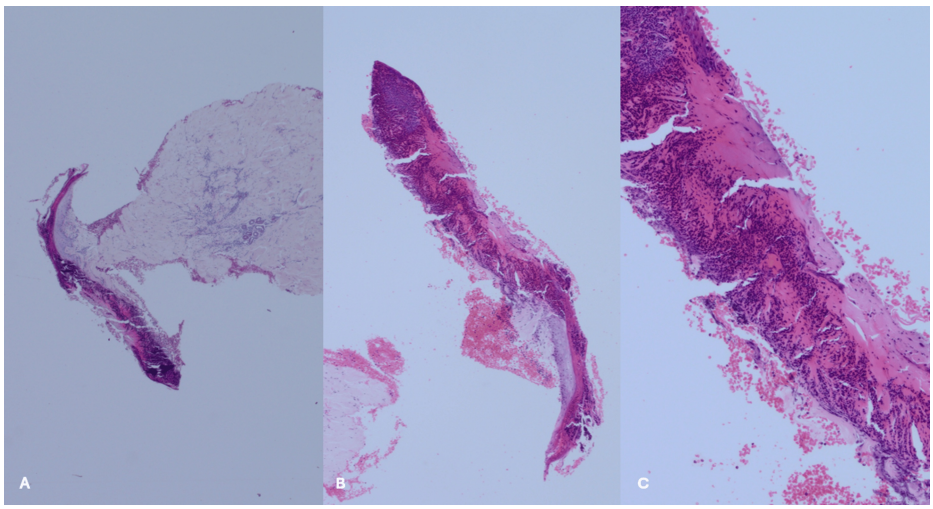


FIGURE 5: Skin punch biopsy histology results: A: Low-power view of the whole specimen showing inflammation within the epidermis; B: Medium-power view showing detached epidermis, which appears mostly necrotic. C: High-power view of necrotic epidermis with extensive inflammation

Management on admission to hospital (month 10)

She was reviewed by her treating oncology consultant and started on intravenous methylprednisolone 2mg/kg daily for one week then 1mg/kg daily for one week then weaned to high-dose oral prednisolone at 100mg daily for three days, followed by a reducing-dose regimen of 50mg, 40mg, 30mg and 20mg daily for three days at each dose. This was followed by 10mg daily for seven days and a final reduction to 5mg daily for seven days before cessation. In total, she completed six weeks of steroid therapy. She completed a five-day course of oral amoxicillin (1 gram three times per day) at the beginning of her hospital admission for superadded bacterial infection as well. She was initially seen daily by tissue viability nurses who assisted with antibacterial washes in the form of Octenisan (potassium permanganate soak was not tolerated due to pain) as well as regular dressing changes.

Her rash improved significantly over the course of her month-long inpatient stay. Discussions with oncology concluded that it would be unsafe to continue or re-challenge with pembrolizumab due to this skin toxicity.

The patient was in agreement to move towards best supportive care. She is now managed under the palliative care team and her skin is continuing to improve (as seen in Figure 6).



FIGURE 6: Healing groin fold one month after the start of a high-dose steroid weaning regimen and intensive wound care

Discussion

As discussed in the introduction, intertriginous eruptions associated with PD1 inhibitors are increasingly recognised. Similarly to our case, Totonchy et al. described an inverse eruption associated with pembrolizumab, presenting with erythematous flexural plaques, erosions and secondary impetiginisation. In their case, the initial clinical presentation raised concern for infection, including cellulitis and early necrotising fasciitis, illustrating the diagnostic challenges posed by these eruptions. Histopathological examination demonstrated psoriasiform epidermal hyperplasia and spongiosis, supporting an inverse psoriasiform pattern [6].

Sethi et al. described a series of patients with PD-1 inhibitor-associated inverse lichenoid eruptions, characterised by deeply erythematous, malodorous and eroded anal genital plaques. Histology demonstrated lichenoid/ interface inflammation, with individual necrotic keratinocytes in some specimens [7]. These cases responded to potent topical corticosteroids, with continuation of immunotherapy possible in selected patients. Collectively, these reports establish that PD-1 inhibitors can produce clinically erosive and inflammatory eruptions in intertriginous sites.

Our case may add to this emerging spectrum but differs in the extent of epidermal damage and the overall histopathological pattern. In our case, the eruption was characterised by extensive necrosis and erosion, with histological examination demonstrating near- complete necrosis of the surface epithelium, scant residual viable epidermis and prominent superficial epidermal neutrophils. There was no convincing lichenoid interface pattern or characteristic psoriasiform epidermal hyperplasia. Negative direct immunofluorescence with no deposition of IgG, IgA, IgM or C3 provided no evidence of an antibody-mediated blistering disorder. These findings support a severe necrotising inflammatory dermatitis rather than a conventional lichenoid or psoriasiform drug eruption.

The differential diagnosis of an extensive erosive intertriginous eruption is broad and includes bacterial and fungal infection, inflammatory dermatoses and severe cutaneous adverse reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. An important diagnostic consideration was whether bacterial infection alone could explain the presentation. The markedly elevated CRP (155mg/L), neutrophilia and heavy growth of penicillin-sensitive Staphylococcus Aureus from the abdominal erosion supported an infective component. However, the patient remained afebrile and haemodynamically stable, with no spreading erythema or warmth on examination. Groin swabs demonstrated only skin flora and mixed colonising organisms. Furthermore, the extensive epithelial necrosis and involvement of multiple intertriginous sites were not obviously explained by uncomplicated superficial bacterial infection. These findings raise the possibility that bacterial infection or colonisation complicated an underlying inflammatory eruption, rather than representing the primary pathological process. Nevertheless, a contributory infective component cannot be excluded.

HS was considered due to the patient's past medical history of this inflammatory condition. After her oncology appointment, she was treated empirically for this with one month of oral lymecycline and daily antibacterial washes but her skin continued to deteriorate despite this. At her subsequent dermatology appointment, HS was considered less likely given the absence of characteristic inflammatory nodules, abscesses, sinus tracts or scarring. Furthermore, histopathology demonstrated extensive epidermal necrosis rather than follicular occlusion, rupture or associated perifollicular inflammation, making this diagnosis less likely.

An interesting finding was the presence of multifocal hypopigmented areas within the affected skin which were noted prior to the development of the erosive eruption. Vitiligo-like depigmentation is a recognised immune-related cutaneous adverse event of PD-1 Inhibitors, particularly in patients treated for melanoma, and this is thought to result from T-Cell-mediated melanocyte destruction [10]. The presence of these changes preceding the acute eruption may raise the possibility of an additional pembrolizumab-associated cutaneous immune manifestation, supporting the hypothesis of an underlying immune-mediated process. This is less readily explained by post-inflammatory pigmentary alteration secondary to the subsequent erosive eruption.

The strengths of this case include the detailed clinical assessment, microbiological investigations and histopathological examination including direct immunofluorescence which helped evaluate alternative diagnoses. The temporal association of the rash starting eight months after commencing pembrolizumab, with progression despite conventional treatment for intertrigo as well as improvement following the start of intravenous methylprednisolone and cessation of pembrolizumab may support association with pembrolizumab. However, interpretation is limited by the non-specific nature of the histological findings and the possibility of concurrent bacterial infection.

Importantly, the therapeutic response cannot be attributed solely to the corticosteroid treatment and pembrolizumab withdrawal, as multiple interventions were initiated concurrently, including high-dose systemic corticosteroids, antibacterial washes, a short course of oral antibiotics, dressings and wound care. Therefore, the clinical improvement is supportive of but not specific for an immune-mediated drug reaction, and this represents a limitation in establishing causality.

As a single case, a causal relationship with pembrolizumab cannot definitively be established, nor can the precise underlying immunological mechanism be determined.

Conclusions

This case describes a severe necrotic and erosive intertriginous eruption suspected to be associated with pembrolizumab. The extent of epidermal damage, together with the clinical presentation and response to immunosuppressive treatment, supports a possible immune-mediated drug reaction, although a contributory infective component cannot be excluded.

The case highlights the importance of considering immune checkpoint inhibitor toxicity in patients presenting with atypical or treatment-resistant flexural eruptions. Early dermatological assessment and skin biopsy may facilitate diagnosis and timely treatment potentially preventing disease progression and significant morbidity.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Katherine Irwin

Acquisition, analysis, or interpretation of data: Katherine Irwin

Drafting of the manuscript: Katherine Irwin

Critical review of the manuscript for important intellectual content: Katherine Irwin

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have

declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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