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| **TITLE OF CASE** |
| ***Treatment of gangrenous digit-threatening paraneoplastic acrocyanosis with vasodilator therapy*** |
| **SUMMARY** |
| A gentleman in his 70s with a recently confirmed diagnosis of transitional cell carcinoma of the bladder, reported a two-month history of discolouration, paraesthesiae and pain in his fingers. On examination, he had peripheral acrocyanosis with areas of digital ulceration and gangrene. Following work-up including autoantibody panel, viral screen, serum electrophoresis and upper limb ultrasound doppler, the patient was diagnosed with paraneoplastic acrocyanosis. He underwent robotic cystoprostatectomy and received adjuvant chemotherapy for the management of his cancer. In parallel to chemotherapy, vasodilatory therapy was administered, including two courses of the iloprost analogue prostacyclin and sildenafil. This resulted in significant improvement in acrocyanosis, gangrene and pain.  |
| **BACKGROUND** |
| Acrocyanosis is well described and relates to vasospasm of the small vessels, underlying the skin, of the extremities in response to the cold. It’s aetiology can be primary or secondary. Primary causes are more common in women with the age of onset being between twenty to thirty years old. It may co-exist with chilblains, erythromelalgia or Raynaud’s phenomenon. Secondary causes are extensive; smoking, connective tissue diseases, neoplasms or arterial diseases being the most common.[1]In young adults where primary acrocyanosis is suspected, minimal investigations are required. Whereas, in older adults with atypical features, which involve pain or asymmetry; a targeted history, examination and investigations are needed. These may include routine observations and baseline blood tests (FBC, CRP and ESR) together with a full autoimmune and immunological screen (ANA, ENA, ANCA, C3/C4, immunoglobulins and plasma electrophoresis). A chest x-ray, nailfold capillaroscopy or skin biopsy may be helpful to rule out an underlying pathological process.[2]For most patients, treatment is not required and conservative measures are employed such as gloves and slippers with avoidance of exposure to cold. If medical treatment is required calcium channel blockers e.g. nifedipine or diltiazem may be used but in clinical practice these have not shown to be very effective.[3] There is also limited evidence for bioflavonoids, nicotinic acid derivatives, adrenergic blockers, topical minoxidil, cyclandelate, rutin compounds and bromocriptine. In secondary acrocyanosis the treatment depends on the underlying cause.We report a case of rapidly progressive paraneoplastic acrocyanosis that resulted in digital gangrene and ulceration. In this case, vasodilator therapy resulted in reversal of acrocyanosis, improvement in symptoms and resolution of digital gangrene. This occurred despite progression of the patient’s underlying malignancy.  |
| **CASE PRESENTATION** |
| Our patient was a gentleman in his mid-70s with a history of haemochromatosis and non-cirrhotic alcoholic liver disease. He presented to urology with a two-week history of visible haematuria. A CT Urogram was concerning for metastatic transitional cell carcinoma of the bladder and this was confirmed on subsequent cystoscopy and histology. Two months later, he underwent a robotic cystoprostatectomy, extended lymph node dissection and ileal conduit formation. Five days following surgery, it was noted he had cyanosed digits. On further review, the patient described a two-month history of discoloured fingers, mainly in the distal areas, with visible skin-breaks and blisters. There was associated paraesthesia and pain which was severe to a degree that he resorted to wearing gloves at night-time. He denied any symptoms suggestive of cutaneous systemic sclerosis or other connective tissue diseases (CTD).On examination, it was immediately apparent that the patient had acrocyanosis (figure 1). In addition, there were areas of digital ulceration and gangrene affecting the right second and third digits. Multiple splinter haemorrhages and leukonychia were also noted. Peripheral pulses were normal.  |
| **INVESTIGATIONS *If relevant*** |
| Investigations revealed a strongly positive anti-nuclear antibody (1:1280 – 1:2560) with a homogenous pattern and chromosome positivity. Extractable nuclear antibodies, rheumatoid factor, anti-cyclic citrullinated peptide and anti-phospholipid tests were negative. ANCA and cryoglobulins were negative and complement levels were within the normal range. The patient had a known IgM Lambda paraprotein which was stable in concentration. A viral infection screen, including hepatitis B, C and HIV, was negative. Upper limb arterial duplex was normal. |
| **DIFFERENTIAL DIAGNOSIS *If relevant*** |
| Raynaud’s phenomenon was considered as a differential diagnosis but felt unlikely given the persistent and aggressive nature of his digital symptoms. Following clinical assessment, the diagnosis of acrocyanosis was made and causes for this were considered. Peripheral vascular disease was excluded through upper limb arterial doppler. Haematological causes including cryoglobulinaemia and anti-phospholipid syndrome, were excluded through a comprehensive haematological panel. Although the patient had a longstanding IgM paraproteinaemia, this was felt to be an unlikely cause of his presentation as the paraprotein had been stable in concentration for more than 5 years. Despite a positive ANA screen, an underlying CTD, such as systemic sclerosis or systemic lupus erythematosus, was unlikely in the absence of clinical signs. The pattern of ANA staining was noted to be non-specific and can be associated with cancer or other conditions including infection or liver disease. Observational data suggest that up to 40% of patients with malignant disease test positive for ANA; with paraneoplastic rheumatic syndromes more commonly seen in those with ANA positivity.[4,5] |

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| **TREATMENT *If relevant*** |
| Whilst the patient was in hospital, five days of the prostacyclin analogue iloprost was administered intravenously. This significantly improved the patient’s symptoms which were mainly pain and paraesthesia. There was also an objective improvement with reduced cyanosis and lack of progression of skin necrosis.  |

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| **OUTCOME AND FOLLOW-UP** |
| Following hospital discharge, the patient had signs of worsening digital ischaemia with acrocyanosis, dry gangrene and sensory changes (figure 2). Two weeks post-discharge, a decision was made to commence oral sildenafil (25mg three times daily) and administer a second five-day course of iloprost. Two weeks afterwards, the patient was reviewed and noted to have a significant improvement in digital gangrene and acrocyanosis. At this time, he was started on single agent carboplatin chemotherapy. Carboplatin was chosen over gemcitabine which has been shown to induce and exacerbate acrocyanosis anecdotally.[6] Alongside oncology follow-up, the patient was regularly reviewed by the rheumatology team. Following a second course of iloprost, there was a significant improvement in his acrocyanosis (figure 3). At this stage, his digital discolouration had almost entirely resolved, the gangrenous areas had reduced in size and his sensory symptoms were improving. The timeline of events is summarised in figure 4. Six weeks after starting carboplatin chemotherapy, a repeat CT thorax-abdomen-pelvis showed interval disease progression with the development of new ascites secondary to peritoneal metastases. Metastases were also noted in the right common iliac node, surgical incision line and the right 6th rib. A decision was made to add gemcitabine to his chemotherapy regime from cycle five onwards. Three months after starting gemcitabine, interval CT imaging showed further disease progression with increasing size of necrotic and cystic lesions in the pelvis and a new thrombus in the inferior vena cava. The patient was subsequently switched to second line immunotherapy and atezolizumab was commenced shortly afterwards and is ongoing. Despite oncological disease progression, signs of peripheral acrocyanosis have continued to improve with resolution of gangrene and improving digital discolouration. He has continued treatment with sildenafil therapy.  |

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| **DISCUSSION *Include a very brief review of similar published cases*** |
| Paraneoplastic acrocyanosis is a manifestation of paraneoplastic acral vascular syndrome (PAVS). PAVS is a rare vascular condition characterised by ischaemia and necrosis, predominantly affecting the hands.[7] Clinically, PAVS appears similar to Raynauds phenomena but follows a much more rapid clinical course and is often associated with gangrene of the fingers.[8] Unlike Raynauds phenomena, PAVS affects an older cohort of patients and affects male and females equally.[6] A diagnosis of PAVS should be considered in all patients presenting with new-onset digital ischaemia as an estimated 15% have underlying malignancy.[8]PAVS has been described in patients with lung, stomach, breast, ovarian, testicular and thyroid malignancy.[7] It is most commonly associated with adenocarcinoma which is described in around 50% of cases.[6] In PAVS, digital ischaemia can precede or follow a diagnosis of malignancy with a median onset of 2 months post-cancer diagnosis reported in one case series.[7] The pathophysiology of PAVS is not fully understood and several mechanisms have been proposed. Several authors have suggested that tumour cells directly produce vasoconstrictive substances.[11] In some cases, tumour antigen-antibody immune complexes may deposit in small vessels, stimulating a vasculitic process.[10,11] When tumour cells infiltrate the cervical plexus, hyperstimulation can result in vasoconstriction due to the release of vasoactive mediators.[10,11] Other proposed mechanisms include microembolism of tumour cells and acquired prothrombotic cogulation abnormalities due to the hypercoagulable state seen in malignancy.[9,10,11] A summary of proposed pathogenic mechanisms is summarised in figure 5.Due to the rarity of PAVS, there is insufficient evidence to define the optimal treatment regime. Vasodilators including prostacyclin, calcium channel blockers and phosphodiesterase inhibitors have been trialled in case series4,. Prostacyclin infusion can improve symptoms in some patients and reports have shown that cancer treatment improves digital ischaemia in around half of cases.[7,9] In some but not all cases of PAVS, cure of the underlying cancer results in resolution of ischaemia.[7] In around 25% of cases, symptoms are refractory, and amputation is sometimes needed.[7]In summary, we have presented a case of paraneoplastic acrocyanosis. Despite cancer progression, treatment with the prostacyclin analogue, ilioprost and sildenafil resulted in reversal of ischaemic changes and a significant improvement in symptoms.

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| **LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*** |
| Acrocyanosis should be considered in patients presenting with atypical symptoms of Raynaud’s phenomena.New onset acrocyanosis should prompt the search for underlying malignancy, particularly in older patients.Prompt and aggressive vasodilator therapy can result in the improvement and reversal of ischaemic changes seen in PAVS. |

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| **FIGURE/VIDEO CAPTIONS** |
| Figure 1Bilateral acrocyanosis with blue discolouration affecting the peripheries of all digits on both hands. Figure 2Progression of acrocyanosis with dry gangrene affecting the tips of multiple fingers.Figure 3Improvement of acrocyanosis following aggressive vasodilatory therapy with intravenous prostacyclin and sildenafil. As illustrated in the figure, the areas of distal gangrene have largely resolved.Figure 4Timeline illustrating the progression and management of bladder cancer in comparison to the development and resolution of peripheral acrocyanosis. K Biddle created this image.Figure 5Proposed pathophysiological mechanisms for the development of paraneoplastic acrocyanosis.[10,11]. K Biddle created this image. |

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| **PATIENT’S PERSPECTIVE** |
| “I found the treatment chosen was very adequate and has been efficient. We could see improvementEverything was well explained and our questions were answered.We were reassured along the process . I was very worried and wandering if I would lose my fingers. It hurt a lot but it was gradually reduced with the treatmentWe feel we were very well treated by everyoneThe fingers are nearly back to normal, now ,it is just the very end of the left index.” |

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