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CASE REPORT

Nicolau syndrome in an athlete following intra-muscular diclofenac injection

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Nicolau Syndrome (also known as Embolia cutis medicamentosa and livedo-like dermatitis) is a rare but severe localized adverse drug reaction to a range of intra-muscular preparations. It manifests as acute pain, cutaneous, subcutaneous and intra-muscular inflammation and necrosis immediately following an injection, with potentially devastating sequelae. We describe the syndrome in a 21-year-old national level race walk athlete following an intramuscular diclofenac injection.

INTRODUCTION

Nicolau Syndrome is a rare adverse reaction to a variety of intra-muscular drug preparations, characterized by severe pain, skin rash and soft tissue necrosis at the site of the injection. Medications known to result in Nicolau Syndrome include Diclofenac, Penicillin, Triple Vaccine and others (*3*). Its consequences can result in significant morbidity for the individual, and significant cost to the medical establishment. While the condition and its cutaneous appearance is well recognised in the dermatological literature, the underlying muscle necrosis is less well described (*8*). Despite abundant case reports, its aetiology and hence management remains speculative (*1-6*). Proposed mechanisms include acute vasospasm, arteritis and thrombo-embolic occlusion of small arteries resulting in end organ damage (*5*).

Intra-muscular Diclofenac is a commonly used anti-imflammatory medication in professional sport, but to our knowledge, no cases of Nicolau Syndrome have been presented in the sports medicine literature. We describe the syndrome in a 21-year-old national level race walking athlete following an intramuscular (IM) injection of Diclofenac.

CASE REPORT

A male, 20-year-old national level race walk athlete presented to our hospital in extreme pain, 75 minutes following the administration of IM Diclofenac to the upper, outer gluteal region, by his team doctor. The injection procedure was described by the practitioner as unremarkable, and the athlete had received Diclofenac injections for leg pain previously. The athlete described an unusually high

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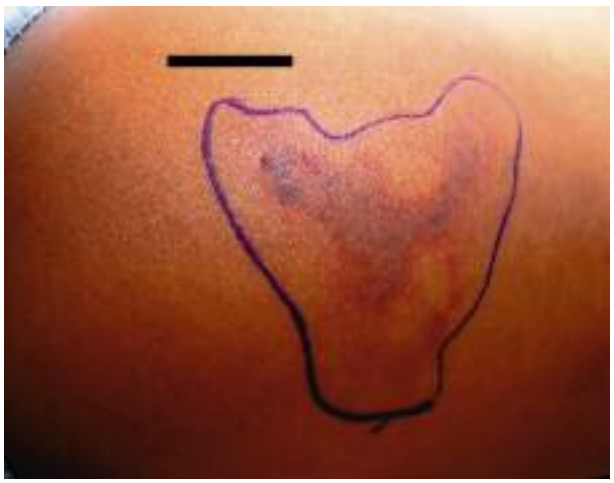

Fig. 1. — Photograph of right gluteal region on day 10 post injection illustrating the nature and extent of the rash. Top left is a small eschar not related to the actual injection site, which continued to enlarge prior to eventually sloughing (Line = 2.5 cm).

level of pain immediately on insertion of the needle and his coach observed more bleeding than he felt was usual. On arrival, ice was applied to the area and intravenous morphine was required to settle his pain.

Immediate assessment revealed a blanching, purpuric rash which evolved rapidly (over hours) to a mottled appearance (fig 1). The athlete felt this may have been the result of placing ice on the area immediately after the event. The area around the injection site was exquisitely tender to palpation and he had pain with any passive or active hip joint movement. Initial differential diagnosis included a local toxic reaction to the Dicolofenac, acute bleeding and acute compartment syndrome. He was started on oral prednisolone and was admitted for IV analgesia.

Very little symptomatic improvement occurred within the first 24 hours, and the gluteus maximus and medius became increasingly tense and painful to palpation. The MRI findings 24 hours post injection can be seen in fig 2. Haematological and biochemical testing revealed an elevated Creatine kinase and myoglobin as well as other markers of muscle damage (fig 3). White cell count, inflammatory markers and renal function were unremarkable at all times.

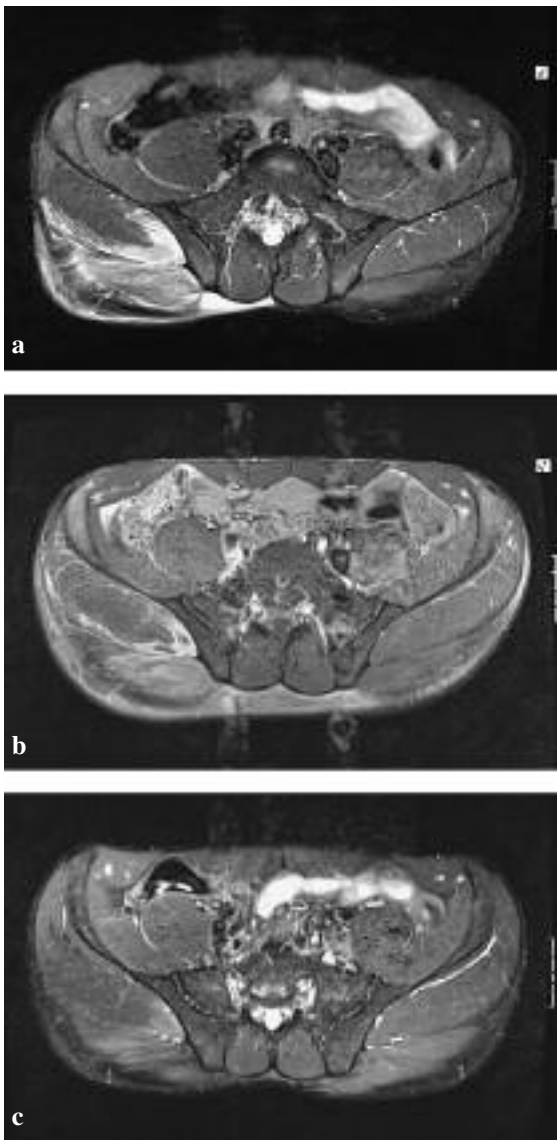

Fig. 2. — a) Inversion recovery axial MR images performed 24 hours after injection show extensive oedema in the subcutaneous fat extending to the midline posteriorly. There is also extensive oedema throughout the superior aspect of the gluteus maximus and the medial aspect of the gluteus medius associated with inter-muscular fluid. The needle track can be seen as a straight high signal line extending to the deep aspect of the gluteus maximus. The T1 weighted images showed no evidence of acute haemorrhage.
b) A follow-up post gadolinium scan was performed at 7 days to look for evidence of focal muscle necrosis. A fat suppressed T1 image shows two small areas of necrosis in the medial gluteus medius. There is low grade enhancement of the residual muscle oedema.
c) A further follow-up scan at 28 days shows a small amount of residual edema. The areas of necrosis seen earlier have now almost completely resolved.

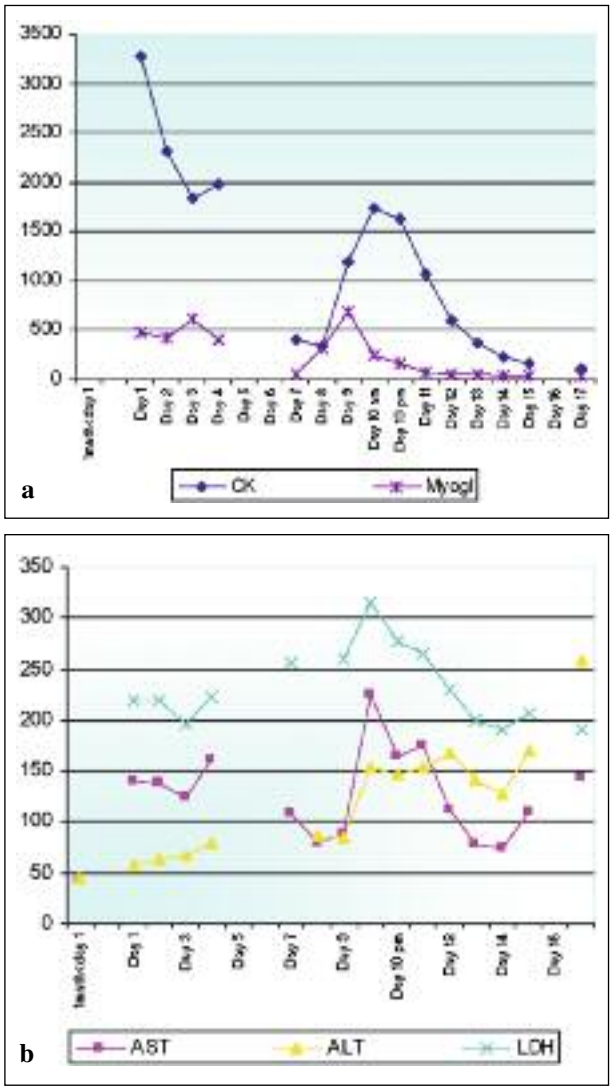

Fig. 3. — Serial Biochemistry a) Creatine Kinase (CK) and Myoglobin (Myo) b) Aspartate Transaminase (AST), Alanine Transaminase (ALT) and Lactate Dehydrogenase (LDH).

By Day three, his pain was still requiring high levels of intravenous and oral analgesia. A diagnosis of acute compartment syndrome was still considered possible, but as he was continuing to gradually improve and his biochemistry was improving, fasciotomy was not performed. Given the uncertain diagnosis, and as a precaution, he was initiated on intravenous Antibiotics (Augmentin) and the oral cortisone was ceased. Physiotherapy concentrating on simple gluteal activation exercises was initiated. By Day five he was starting to mobilize around the ward, despite an ongoing tense palpable mass in his gluteal region and at his request he was discharged after 6 days. On review at day nine post injection, he was continuing to do well, and against advice competed in a 10 km walking race that afternoon. Upon completion of the race his gluteal region was once again exquisitely painful, tense, and his erythematous rash had progressed (fig 3). He was readmitted for IV analgesia and blood assessment revealed a progression of his CK and myoglobin levels. Repeat MRI demonstrated areas of muscle necrosis within the gluteus medius (fig 2-b).

He made slow progress until Day 13 when a diagnosis of Nicolau Syndrome was considered and despite a negative D-dimer test, he was started on subcutaneous low molecular weight heparin. Subsequently he made rapid progress and by day 16 he was discharged walking with only a mildly antalgic gait, and with a marked reduction in his local tenderness. Anticoagulation was ceased at discharge.

On follow-up at Day 22 he was walking pain free but continued to have a tender, tight muscle band through his gluteus medius and maximus. He was instructed to continue a graded progression back to activity and on review at Day 30 he was walking pain free, had minimal tenderness and his rash had almost completely resolved. He was cleared to resume full training and at follow-up at six weeks he had resumed competing with no further problems.

DISCUSSION

Nicolau Syndrome (also known as Embolia cutis medicamentosa) has been recognized for many years as an adverse drug reaction at the site of an IM injection (*8*). It has been reported following a wide variety of injections and while rare, it is well recognized following anti-inflammatory injections (*1-6*). It is characterised by severe pain following IM injection with associated skin changes. Necrosis and secondary infection of the skin and underlying muscle may follow, often requiring extensive debridement and with significant morbidity (*1,3*).

Nicolau Syndrome is well described in the dermatological literature, with the majority of case reports concentrating on the cutaneous and subcutaneous manifestations (*1,2,3,4,6*). While underlying muscle damage has received less attention, delayed muscle necrosis has been described (*8*). This athlete presented with typical pain and a livedoid type rash, which was initially mistaken for a reaction to ice pack application. However, while the cutaneous manifestations were concerning, it was the underlying muscle injury which was most marked. MRI revealed extensive increased signal intensity reflecting intra- and extra-muscular inflammation and oedema, well beyond the actual infiltration of the injection. Over several days there was a progressive change in imaging appearance consistent with intramuscular and subcutaneous inflammation, which gradually resolved, concurrent with an improvement in symptoms. These imaging changes were mirrored by the marked elevation in muscle enzymes with peaked immediately following the injection and after his premature return to physical activity.

The initial clinical improvement observed with rest, oral cortisone and antibiotics was mirrored by normalizing biochemistry and imaging findings. Premature return to intense activity resulted in a worsening of both cutaneous and intramuscular symptoms and signs. This was again reflected in both the biochemistry and imaging, with the latter revealing small areas of intramuscular necrosis in the gluteus medius. Despite the radiologically observed areas of necrosis, the athlete underwent a full recovery with no residual muscular symptoms and signs, and only a small area of skin hypopigmentation under the sloughed eschar. This is in contrast to the literature which uniformly tends to suggests a more guarded prognosis (*1,2,3,4,6*).

In this case there was a delay in recognising the syndrome as the clinical appearance was one of a local toxic reaction, acute haemorrhage or acute compartment syndrome. Despite the suspicious presentation, surgical fasciotomy was delayed as there was sufficient uncertainty as to warrant caution. Clinical differentiation alone was difficult and the regular imaging and biochemical monitoring assisted in the clinical decision not to proceed to surgery. Of note, he was treated empirically with ice, which may be ill advised, given the suspected vascular aetiology and has been suggested to aggravate the condition (*8*). This athlete appears to have been fortunate, given his initial management with ice being associated with worsening outcomes. Oral corticosteroids were initiated immediately and with this approach having been shown to have a positive effect, it is possible that this was responsible for his rapid initial improvement.

The pathogenesis of Nicolau syndrome remains uncertain. Sympathetic stimulation and subsequent vascular spasm from peri-arterial or peri-neural injection, or inflammatory and thombo-embolic end arterial reactions to intra-articular injection are commonly touted mechanisms, but there is little evidence for any of these (*5,7*). Crystalisation of aqueous drugs in the vessels and arteriovenous shunt development are other proposed causes (*5*). The end result of this vascular compromise is end-organ damage to muscle, cutaneous and subcutaneous tissues. McGee and Davison report on two cases of skin necrosis following non-steroidal anti-inflammatory injection, with histology revealing dermal and subcutaneous necrosis with focal thrombosis and inflammation (*6*). They feel that in their cases it was likely that this resulted from subcutaneous rather than intramuscular injection, and highlight the difficulties in giving an intra-muscular injection. In this case, it was most unlikely that the injection was subcutaneous (as the athlete had a very low body mass index), but given the immediate report of pain, and possibility of increased bleeding, it is possible that the injection was either intra- or peri-vascular. Therefore, practitioners utilizing intra-muscular diclofenac injections should not only be aware of the importance of intramuscular versus subcutaneous injection (*5*), but also of the risk of vascular and peri-vascular injection.

The diagnosis of Nicolau Syndrome in this case is based purely on the clinical picture and its correlation with previous case reports, as there is no confirmatory test available. For the first time, we have described the intra and peri-muscular involvement of muscle in Nicolau Syndrome and correlated symptoms with both imaging and biochemistry. This young athlete had an excellent outcome with a

broad spectrum of treatment including oral corticosteroids, antibiotics and low molecular weight heparin. It is unclear which of these treatments was the appropriate approach, or whether these affected the natural history of the condition, but all have some foundation in the literature. Given the rare, although potentially severe consequences of intramuscular diclofenac, practitioners managing athletes should consider both the indications and consenting procedures prior to its use. Futhermore, Nicolau Syndrome should be considered a diagnostic possibility for anyone presenting with severe localized pain following an intramuscular injection of any substance.

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