Naltrexone-induced Nicolau syndrome masquerading as cutaneous abscess

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SUMMARY

Nicolau syndrome—also known as Embolia Cutis Medicamentosa—is a rare complication of intramuscular and subcutaneous injections manifesting as necrosis of skin and the underlying tissues. The exact pathogenesis is uncertain. There are several hypotheses including direct damage to the end artery, cytotoxic effects of the implicated drug or additives in the injectable preparations. Naltrexone is a long-acting opioid antagonist used primarily in the management of alcohol and opioid dependence. The patient received intramuscular naltrexone for treatment of alcoholism. A week later, she presented with what appeared to be cellulitis at the site of injection. It progressed in spite of antibiotics and mimicked an abscess. Attempted incision and drainage however yielded no pus. Deep tissue necrosis was seen and histopathology was consistent with Nicolau syndrome. As per our knowledge, this is the first reported case of naltrexone associated Nicolau syndrome that masqueraded as a buttock abscess.

BACKGROUND

Nicolau syndrome is a rare, adverse reaction causing tissue necrosis at the site of intramuscular injection. Naltrexone is a potent agent approved by the US Food and Drug Administration for treatment of alcohol addiction and opioid dependence. With expected increased use of this product for these two indications, we feel it is important to watch out for Nicolau syndrome—a rare complication of intramuscular injection.

CASE PRESENTATION

A 50-year-old Caucasian woman presented to her primary care physician with a history of pain, swelling and redness in the region of her right buttock. Her symptoms started 1 week after she received an intramuscular injection of naltrexone as part of treatment for alcohol dependence. She denied fever, chills and other systemic symptoms. Her medical history was significant for alcohol abuse and Raynaud's syndrome. She was empirically treated with cephalexin for suspected cellulitis. When her symptoms did not improve, an ultrasound of the area was obtained. It did not identify any definite abscess. Cephalexin was discontinued and she was switched to amoxicillin-clavulanate (augmentin). Further deterioration prompted a referral to infectious diseases for intravenous antibiotics. At this time, local examination revealed erythema, swelling and tender induration with central necrosis (figure 1). Further evaluation of the area with a CT scan revealed a well-defined area of soft tissue inflammation with central gas collection, suggestive of an abscess (figure 2). Incision and

Figure 1 Erythema, swelling and tender induration with central necrosis.

drainage was attempted, but yielded no pus. Thick pasty material suggestive of fat tissue necrosis was extracted from the area. This material was sent for histopathology as well as microbiology cultures.

INVESTIGATIONS

Histopathology revealed fibro-adipose tissue with fat necrosis and predominantly eosinophilic infiltrate (figure 3). Bacterial, fungal and mycobacterial cultures were negative.

TREATMENT

Antibiotics were discontinued and she underwent wide excision of the necrotic area.

OUTCOME AND FOLLOW-UP

Over the following 6 months she underwent two more surgical debridements and the area healed completely leaving behind a puckered scar (figure 4).

Figure 2 CT scan showing (arrow) well-defined area of soft tissue inflammation and possible abscess.

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Figure 3 Excision biopsy revealing fibro-adipose tissue with fat necrosis with predominantly eosinophilic inflammation.

DISCUSSION

Naltrexone is an opioid receptor antagonist with relatively selective competitive antagonism at mu-opioid receptors used primarily in the management of alcohol and opioid dependence. It has demonstrated efficacy at decreasing heavy drinking, promoting abstinence and decreasing relapse in alcohol dependent subjects.^{1 2} Long-acting depot formulations of naltrexone have been shown to be safe and effective in the treatment of alcohol dependence.³ Ray *et al*⁴ have reviewed the detailed mechanism of action in the treatment of alcoholism. It is a potent agent in the treatment of alcohol dependence, and it was approved in 2006 by the US Food and Drug Administration for this indication. In addition, in 2010 naltrexone was approved for use in the treatment of opioid dependence⁵ with resultant increased use of this product for these two indications.

Nicolau syndrome also known as Embolia Cutis Medicamentosa is an uncommon complication of intramuscular injection leading to variable degrees of necrosis involving skin, subcutaneous tissue, and even muscle at the site of intramuscular injection.⁶ It was first described in the 1920s, following delivery of bismuth salts for treatment of syphilis. Clinical features of this syndrome were elaborated by Freudental in 1924 and Nicolau in 1925.^{7 8} The phenomenon has been reported in association with the administration of a variety of medications including diclofenac,⁶ penicillins,^{6 9} vitamin K¹⁰ and etanercept.¹¹ The typical presentation is blanching and pain around the injection site soon after injection, followed by erythema, livedoid patch, haemorrhagic patch and finally tissue necrosis. Repetitive cycles of wound breakdown and partial healing are typical. The exact pathogenesis is uncertain, but there are several

hypotheses. It could be attributable to direct damage to the end artery or it may be secondary to cytotoxic effects of a particular drug or the additives in the injectable preparation.^{8 12} Management involves radical excision of necrotic tissue. This is important because inadequate debridement leads to poor wound healing.¹³ Hence, CT scan or MRI is needed to determine the extent of tissue involvement.

The patient developed naltrexone associated Nicolau syndrome in her buttock area. Clinically, it masqueraded as a soft tissue infection that was not responding to antibiotics and hence she underwent an incision and drainage of a suspected abscess. Surprisingly, no pus was detected, but instead fat tissue necrosis was seen. Histopathology was consistent with features of Nicolau syndrome and microbiology cultures were all negative. It is a matter of speculation about how much the patient's underlying Raynaud's syndrome may have contributed to this unusual tissue reaction to the intramuscular injection. While histology changes of tissue necrosis have been described in the literature following removal of naltrexone depot implants,¹⁴ ours is the first case report of Nicolau syndrome following single dose injection of naltrexone. With the increasing use of this product, clinicians should be aware of the risk of Nicolau syndrome—a very uncommon, but dramatic and disfiguring complication.

Learning points

- ▶ Nicolau syndrome is a rare complication of intramuscular injection.
- ▶ This may appear as subcutaneous abscess, but is actually associated with sterile tissue necrosis. Antibiotics did not help and this condition requires extensive surgical debridement.

Competing interests None.

Patient consent Obtained.

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Figure 4 Puckered scar.

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