Acute Transverse Myelitis and Nicolau Syndrome after Benzathine Penicillin Injection

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Abstract
Rare complications have been documented due to inadvertent intravascular administration of penicillin such as Nicolau syndrome (lipoatrophy), transverse myelitis, injury to sciatic nerve as well as Hoigne syndrome (transient central nervous system dysfunction). We present a case report where a young male developed Nicolau syndrome and transverse myelitis after receiving benzathine penicillin injection.

Introduction
Alexander Fleming discovered penicillin in 1928, a potent antibiotic that has saved many lives. At that time little was thought of the possible adverse reactions it can have. Acute transverse myelitis and Nicolau’s syndrome are known but rare complications of Penicillin but their occurrence together is a rarity.

Case Report
A 20 year old male was admitted with complaints of severe pain in his right buttock after receiving intramuscular Benzathine penicillin injection following which he developed sudden and complete weakness of both lower limbs and loss of sensation in both lower limbs below the umbilicus. He was a known case of rheumatic heart disease with mitral stenosis who had undergone a balloon mitral valvotomy in 2006 and was on intramuscular benzathine penicillin prophylaxis 1.2 million units every 21 days since 2006. He also suffered from Ankylosing spondylitis and was on sulphasalazine. On central nervous system examination he was conscious oriented, higher mental functions were normal, cranial nerves examination was normal, power was 0/5 in lower limbs and 5/5 in upper limbs, tone was decreased in lower limbs. The patient reported approximately fifty percent decrease in touch pain and temperature sensations upto the T-10 dermatome. Ankle reflex was absent on admission but could be elicited 12 hours after the admission. Plantar reflex could not be elicited. On cardiovascular examination he was found to have a loud S1 and mid –diastolic murmur in the mitral area. The respiratory and per abdomen examination was normal. He had no bladder or bowel involvement. Patient was administered Inj. Methylprednisolone 1000mg, after 4 hours power improved to 3/5 in both limbs and after 12 hours power was 4+/5 and it remained the same till his discharge. He also had complaints of hyperaesthesias in his lower limbs. At the site of the injection patient had developed purplish discolouration (Figure 1). The patient was found to have developed Nicolau syndrome following the injection Benzathine Penicillin. The patient was continued on intravenous Methylprednisolone therapy for 5 days and started on oral Prednisolone (1 mg/ kg).

He underwent MRI dorso-lumbar spine after 2 weeks and was found to have changes in the vertebral region which could be attributed to Ankylosing spondylitis but the spinal cord was normal. Nerve conduction studies revealed bilateral, asymmetric (right>left ) motor axon degeneration affecting L₅, S₁, L₁₂, D₁₂ fibres, most likely to be a presentation of an acute radiculomyelitis with reflexes preserved in a denervated muscle.

The steroids were tapered after 2 weeks and stopped and the patient was discharged. The patient’s sensory complaints partially responded to amitryptiline and pregabalin. Oral anti-histaminics and antibiotic ointment for local application was prescribed.

Causality assessment done as per the Naranjo scale, revealed that the patient had a score of seven which made it a probable adverse reaction and this was reported to the pharmacovigilance centre at our college. On follow up after 8 months he continues to have a power of 4+/5 and all reflexes are present. He has developed wasting of right calf muscle but is able to walk without support. But there is no significant improvement in his sensory complaints.

Discussion
Inspite of the worldwide use of benzathine penicillin G, events related to accidental intra-arterial injection do occur and have an adverse outcome. Most cases are described in children aged 6 and 12 years. Few cases have been reported in adults. This is probably related to the fact that the use of the benzathine penicillin G is more common in children. In all cases described in the literature, the medication was given in the upper outer quadrant of the buttock just like in our patient. The types of injuries include semicircular-lipoatrophy, sciatic neuropathy, genital gangrene gangrene of ipsilateral or contralateral feet and transverse myelitis.

Many mechanisms have been proposed for transient neurological dysfunction. The first explanation is that the frequency of gluteal injuries suggest that the mechanism is inadvertent injection into branches of the superior gluteal artery located in the upper outer quadrant. Some authors hypothesized that penicillin suspension injected into the superior gluteal artery under high pressure could flow retrograde into the internal iliac artery and then to the aorta, leading to obstruction of the lumbar
spinal arteries. In the thoracolumbar region, all of the blood supply to the spinal cord is derived from a single artery from the aorta, the artery of Adamkiewicz. The retrograde flow could extend further up the aorta to the level of the artery of Adamkiewicz. From that vessel, the product would pass into the anterior spinal artery and result in transverse myelitis. Obstruction of this vessel could be expected to result in a cord lesion between T9 and T12. Others authors postulated that the drug can produce arterial vasospasm when injected to the arteries. But this mechanism is unlikely. First, the reported injuries are too distant. Second, some injuries have been duplicated in rabbits with intraarterial but not periarterial injection. These results strongly suggest that tissue damage produced by penicillin is secondary to the intra-arterial administration of the drug.

Vascular injury may be the result of microemboli of the injected crystals of the penicillin salts. Embolization of other ingredients or allergic reactions to them could play a role (sodium citrate, carboxymethylcellulose, polyvidone). Because the benzathine benzyl penicillin injectable suspension is viscous and opaque, it would hinder the visualization of blood on aspiration.

Nicolaus syndrome (NS) is a rare injection site reaction, following intramuscular administration of drugs, with varying degrees of tissue damage. It is synonymously described as embolia cutis medicamentos and livedoid dermatitis. The typical presentation is intense pain around the injection site soon after injection, followed by erythema, purplish discolouration of the skin, haemorrhagic patch, and finally tissue necrosis. Subsequently, it results in cutaneous, subcutaneous, and even muscular necrosis with a pale marble-like livedoid pattern. Our patient had skin changes and subcutaneous fat atrophy, without any wound. The first description of this condition was made by Freudenthal and Nicolaus in 1924 and 1925. Initially seen with intramuscular bismuth salt administration in syphilis, it has now been documented with several drugs (Table 1). The mechanism of NS is not fully understood, but one hypothesis is damage to the end-arteries by cytotoxic effects following intraarterial embolism of the particular drug, followed by arterial vasospasm (probably secondary to release of some vasoactive mediators) and tissue necrosis. Other hypothesis is extra arterial compression of the supplying artery by the injected volume. But none of these hypotheses justify occurrence of NS after other routes of administration of drugs such as intraarticular injections. In general, NS is a catastrophic vascular phenomenon that should be differentiated from nerve injury or local pure immunologic reactions secondary to injected materials.

Tissue diagnosis is based on skin biopsy showing necrosis of dermis and subcutaneous tissue and muscle biopsy showing focal vascular thrombosis and inflammatory infiltrate in acute phase. There is no published standard of care for management of NS and treatment used ranges from local care to extensive surgical debridement. A combination of surgical debridement, oxygen therapy, heparin and broad spectrum antibiotics should be employed as therapy. Vasospasm may be relieved by the phosphodiesterase inhibiting action of pentoxyphylline. Topical corticosteroids are effective for acute tissue inflammation. Wound care, debridement, dressings, and flap reconstruction are ideal surgical measures. Failure to recognize the extent of fat necrosis and poor blood supply leads to inadequate debridement and poor wound healing. The patients are then prone to repetitive cycles of infection leading to extensive scarring, soft tissue indentation, and unsightly skin grafts.

Although still rare, this disastrous complication can be prevented by simple precautions. In intramuscular injections, the needle must be long enough to reach the muscle: a 90-kg patient requires a two-inch needle whereas a 45-kg patient requires a 1.25-1.5-inch needle. The Z-track method of injecting can minimize subcutaneous irritation following intramuscular injection. When multiple injections have to be given, different sites should be chosen. Before injecting, one should always aspirate and look for blood; one should immediately stop if the patient complains of pain on injecting. In conclusion, clinicians should be aware of NS and transient neurological dysfunction, two serious complications of the intramuscular injection of common agents such as penicillin.

Conclusion

We report this case to highlight the occurrence of two rare and serious complications that occurred simultaneously in a patient to a widely used drug and to sensitize the clinicians to take preventive measures to avoid any such occurrences.

Table 1: Drugs associated with Nicolaus syndrome

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Diclofenac, Ibuprofen, Ketoprofen, Piroxicam</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Penicillin, Sulphapyridine, Tetracycline, Steptomycin, Sulphonamide, Gentamicin</td>
</tr>
<tr>
<td>Steroids</td>
<td>Dexamethasone, Triamcinolone</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>DPT vaccine, Diphenhydramine, Lidocaine, Phenytoin, Etanercept</td>
</tr>
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NSAIDs= Non-steroidal anti-inflammatory drugs

References