TWO DIFFERENT CASES OF NEW ONSET NEUROPATHY AFTER PANCREATIC TRANSPLANTATION

Dr. Vedhanayagam Nagarathinam¹, Dr. Dhanaraj², Dr. Nikhil³, Dr. Anil Vaidya⁴

¹Consultant Neurologist, Kongunad Hospitals, Tatabad, Coimbatore
²Consultant Neurologist, Apollo Main Hospitals, Greams Road, Chennai
³Apollo Main Hospitals, Greams Road Chennai
⁴Apollo Main Hospitals, Greams Road Chennai

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Corresponding author: Dr. Vedhanayagam Nagarathinam
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Abstract:
Presenting two different cases of new onset peripheral neuropathy after pancreatic transplantation. One demyelinating in type which is rare in literature, recovered spontaneously and other one is axonal in type improved with early aggressive intra-venous immunoglobulin therapy.

Keywords: Tacrolimus, Post transplant, IV-IG(Intravenous immunoglobulin), Demyelinating and Axonal neuropathy

Introduction:
Pancreatic transplantation is the most logical treatment for diabetes mellitus and most of the type-one diabetes mellitus patients are known to have symptomatic peripheral neuropathy prior to the pancreatic transplantation. It is known that these symptoms improve after pancreatic transplantation.¹,² New onset neuropathy following pancreatic transplant is extremely rare, it might occur secondary to an independent problem or drugs which are given for immuno-suppression. This paper describes two different patients with peripheral neuropathy after pancreatic transplantation.

Case Report 1:
A 22 year male presented with subacute onset, progressive symmetric weakness and numbness of all four limbs for two month duration. On clinical examination patient had moderate weakness (walks with someone’s help) and graded sensory loss of all modalities involving both upper and lower limbs, with no clinical evidence of autonomic involvement.

He was a known type one diabetes for ten years on insulin therapy. He had no symptoms of peripheral neuropathy, retinopathy or nephropathy before transplant. He underwent isolated pancreatic transplantation, two months prior to the onset of these symptoms. He received booster dose of HBV vaccine preceding surgery and 15 mg of Adalimumab on the day of surgery. Post operatively he was on mycophenolate 1gram/day and tacrolimus 1.5mg/day. He was ambulant until this presentation. Electrophysiological study and other tests were done to evaluate the cause of neuropathy are mentioned in Table 1. Tacrolimus was discontinued and an alternative immunosuppression cyclosporine was initiated. Patient had progressive improvement in a week without any active medical intervention.

Case Report 2:
A 23 year old gentleman, presented with sub-acute onset, progressive weakness and paraesthesias of all four limbs of one month duration. Clinical examination revealed moderate weakness of all four limbs with bilateral foot drop and sluggish deep tendon reflexes along with graded sensory loss for all modalities.

He was a known type one diabetic for 10 years on insulin therapy. He also had no symptoms of peripheral neuropathy, retinopathy or nephropathy before transplant. He underwent isolated pancreatic transplant five months prior to the onset of the present symptoms. He received a booster dose of HBV vaccine preceding surgery, and 15 mg of Adalimumab on the day of surgery. Post operatively he was on mycophenolate 1g/day and tacrolimus 1 mg/day. Electrophysiological study and other investigations were mentioned in Table 1. Tacrolimus was stopped and cyclosporine was initiated as an alternative. However the symptoms deteriorated further hence treated with Intra-venous immunoglobulin for 5 days.
Patient showed improvement in weakness and walks independently within a month.

Table 1: Summary and Investigations

| SUMMARY                        | CASE I                                  | CASE II                                 |
|--------------------------------|-----------------------------------------|-----------------------------------------|
| Age,sex                        | 22 year, Male                           | 23 year, Male                           |
| Duration of Type1 diabetes mellitus | 10 years                               | 10 years                               |
| Glycemic control               | Well controlled                         | Poorly controlled                       |
| Pre-operative evaluation       | No neurologic deficit                   | No neurologic deficit                   |
| Time Duration between Pancreatic Tx and onset of neuropathy | 2 Months                               | 5 Months                               |
| Pre-op vaccine                 | HBV                                     | HBV                                     |
| Per-op medication              | Adalimumab 15 mg single dose            | Adalimumab 15 mg single dose            |
| Post-op immunosuppression      | Tacrolimus 1.5 mg/day                   | Tacrolimus 1.5 mg/day                   |
| Serum Tacrolimus               | 6 ng/dl (5-15 ng/ml)                    | 8.1 ng/dl (5-15 ng/ml)                  |
| Serum B12                      | 355 pg (200-900 pg)                     | 416 pg (200-900 pg)                     |
| Serum TSH                      | 4.5 ng/dl (0.45-4.5 mU/L)               | 4.7 ng/dl (0.45-4.5 mU/L)               |
| ANA, pANCA, cANCA              | Negative                                | Negative                                |
| Serum Protein Electrophoresis  | Normal                                  | Normal                                  |
| CMV-PCR                        | Negative                                | Negative                                |
| CSF Analysis:                  | Cell Count: No cells                   | Cell Count: 10                         |
|                                | Type: Nil                               | Type: Lymphocytes                      |
|                                | Protein: 37 mg/dl                       | Protein: 59 mg/dl                       |
| Electro-physiology             | Demyelinating polyradiculoneuropathy    | Severe sensorymotor polyradiculoneuropathy |
| Treatment given:               | a) Tacrolimus changed to cyclosporine   | a) Tacrolimus changed to cyclosporine   |
|                                | b) Supportive care                      | b) Intravenous immunoglobulin 0.4 g/kg/day for 5 days |
| Outcome:                       | Improved (within a week) after discontinuing tacrolimus | Improved (within 30 days) after discontinuing tacrolimus and early aggressive immunomodulation with IVIG |

Discussion:

New onset neuropathy after transplant procedure is very rare. Etiology for these scenarios can be (i) Surgical procedure related nerve injury, (ii) Focal compressive neuropathy, (iii) Opportunistic cytomegalovirus (CMV) related neuropathy, (iv) Nutritional deficiency, (v) Graft versus host disease (GVHD) manifesting as acute/chronic inflammatory demyelinating polyneuropathy (AIDP/CIDP), (vi) Critical illness myoneuropathy and (vii) Immunosuppressive agents used after transplant. In both of our cases, there was no prior neurological illness or any evidence of graft vs host reaction on
follow up visits. Clinically and by investigations there was no evidence of nutritional deficiency. Post transplant CMV related neuropathy can be a possibility but in both cases CMV PCR test was negative.

The other possibility to be considered would be a neuropathy secondary to the immunosuppressive agents which are used in these scenarios. In our cases, single dose of adalimumab was used per-operatively but this drug and the dose provided is not commonly known to cause peripheral neuropathy.

The tacrolimus related neuropathy was the next possibility. The time between initiation of tacrolimus and onset of symptoms varied between 8 days to 3 weeks. Tacrolimus-related polyneuropathy patients had improvement after switching it to an alternative immunosuppression. Hence in both these patients it was stopped and an alternative immunosuppressive agent was initiated. It is known that exceeding levels of tacrolimus in serum are known to cause peripheral neuropathy. But in both cases the serum levels of this drug were well within therapeutic range, i.e., not exceeding the toxic range. As per Gunnela Norden et al. case report, even with therapeutic levels of tacrolimus peripheral neuropathy can be expected to occur. Hence, high index of suspicion will help in early diagnosis and better management of Tacrolimus related neuropathy Tacrolimus related neuropathy are thought to be due to its direct neural toxic effect. Predominantly, they are axonal in type and most of them recover gradually after discontinuing tacrolimus. Even though, few of demyelinating neuropathy also had been reported in western literature. Our first case presenting with demyelinating type of neuropathy which improved gradually after discontinuing tacrolimus without any further intervention. The second patient with axonal neuropathy, despite of stopping tacrolimus deteriorated quickly and required early aggressive therapeutic intervention with immunoglobulins. Hence we postulate, that in an already vulnerable patient, we need to keep track of the disease progression for early aggressive therapeutic intervention with IVIG.

**Conclusion:**

Even therapeutic levels of tacrolimus can produce both demyelinating and axonal type of progressive peripheral neuropathy. Early discontinuation and switching it to an alternative safer drug would be the first move, followed by, to keep track of the disease progression for early aggressive therapeutic intervention with intravenous immunoglobulin (IVIG).

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