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CASE REPORT

First case of insulin neuritis after islet transplantation

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Insulin neuritis, recently renamed "Treatment-induced neuropathy of diabetes" (TIND), is a rare iatrogenic complication first described in 1933 by Caravatti, and more recently characterized by Gibbons [1]. It presents as an acute, painful, and autonomic neuropathy occurring within 8 weeks in patients with chronic hyperglycemia in whom rapid glycemic improvement is achieved by dietary restriction or hypoglycemic agents [1]. Although known to dramatically improve glycemic control, pancreas or islet transplantation has never been reported to cause TIND.

We report the case of a 35-year-old female with a 23-year history of type 1 diabetes presenting with brittle diabetes despite sensor-augmented pump therapy. She had proliferative retinopathy with vitreous hemorrhage, treated by panretinal photocoagulation 5 years previously, and considered stable at the time of transplantation; microalbuminuria (190 mg/24 h) with normal renal function; painful distal neuropathy well controlled by pregabalin. Autonomic dysfunction was diagnosed with symptomatic orthostatic hypotension, mild postprandial nausea, and heaviness treated by domperidone. There was no post-void residual volume. Due to an extreme fear of hypoglycemia and emotional exhaustion, HbA1c levels had been between 10 and 16.7% (86 and 159 mmol/mol) for the previous 2 years with 0.39 Insulin Unit (IU)/kg.

After providing informed consent, the patient was enrolled in the TRIMECO trial (NCT01148680), which was approved by the local ethics committee in accordance with the ethical standards. She received an islet infusion on 04/23/2012 (290,208 IEQ (islet equivalents), 5200 IEQ/kg). The immunosuppressive regimen consisted of mycophenolic acid and tacrolimus with thymoglobulin induction and etanercept during the induction period. HbA1c dropped from 16.7% (159 mmol/mol) to 6.8% (51 mmol/mol) within 2 months (Fig. 1). Ten days after transplantation, she presented with acute, worsening painful neuropathy extending to the four limbs, diffuse hypoesthesia, and ataxic gait, confirmed by nerve conduction studies showing severe sensitive axonal neuropathy, poorly responsive to maximal doses of pregabalin, duloxetine, venlafaxine, amitriptyline, and opioids. At 1 month, she complained of dysuria (echography revealed 200 ml post-void residual volume with poorly contractile bladder requiring self-catheterization), diarrhea, vomiting, and dysphagia, with functional renal failure. Video-capsule endoscopy showed prolonged esophageal transit time with severe motility disorders on manometry, severe gastroparesis confirmed by scintigraphy, and a short small bowel transit time. Blood pressure dropped from 110/70 mmHg lying, to 75/45 mmHg standing, with episodes of syncope. Intravitreal hemorrhage occurred despite previously stabilized retinopathy. Several explorations ruled out the other diagnoses including CMV, EBV and BK virus infections, and vitamin B12 deficiency. The patient refused muscle and nerve biopsy. Symptoms remain unchanged after immunosuppressive therapy switch to sirolimus + tacrolimus, cyclosporine + azathioprine, or belatacept.

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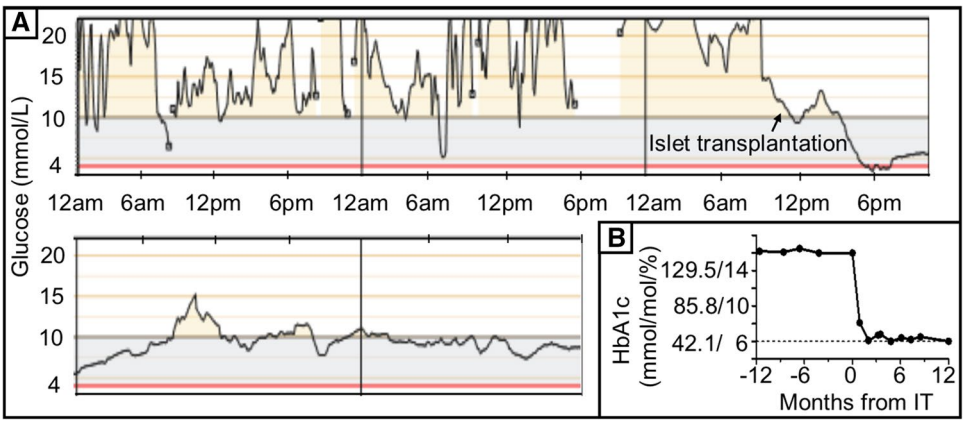

Fig. 1 Glycemic parameters before and after islet transplantation (IT). **a** Continuous glucose monitoring 2 days before and after IT. **b** HbA1c

During the year following transplantation, the patient remained on insulin pump therapy with a low basal rate (4U/day) and fixed small boluses (2U per meal). HbA1c levels were below 6.5% (48 mmol/mol) without hypoglycemia. After 1 year, the patient asked for a second islet transplantation to achieve insulin independence, in accordance with the study protocol. The trial scientific committee considered that the risk of worsening neuropathy after a second islet infusion was low, since the glycemic control was already excellent. The patient finally received a second and third islet infusion, 18 and 24 months after the first one. Insulin could be stopped soon after the third transplantation and the patient remained insulin free for 1 year.

After 6 year follow-up, the islet graft is functional (HbA1c = 6% (42 mmol/mol) with low insulin requirements (0.18 IU/kg), and no hypoglycemia), but symptoms of severe neuropathy have not decreased. The patient requires bladder self-catheterization and intravenous hydration (3 L/16 h) for severe diarrhea and vomiting despite intrapyloric botulinum toxin injections.

Long-term studies in diabetic retinopathy described stabilization after pancreas transplantation, or even improvement of the disease, but the early worsening retinopathy may occur [2]. Studies to date have not reported acute worsening neuropathy after islet or pancreas transplantation, but rather, long-term stabilization, whereas symptoms increase in non-transplanted patients [3]. However, in 2001, Dyck et al. described "an increased weakness" diagnosed by higher Neuropathy Impairment Score and Neuropathy Symptoms Score at 3 months after pancreas and kidney transplantation compared to baseline [4]. As electromyography showed the improvement of conduction abnormalities, the authors concluded that there was development of myopathy rather than worsening neuropathy. Prospective studies with the early neurological evaluations in the post-transplant period are required, including assessment of the association with the decrease in HbA1c.

Our observation is consistent with the diagnosis of TIDN as described by Gibbons based on the acute onset (within 8 weeks) after a rapid and dramatic decrease in HbA1c (more than 2% over a period of less than 3 months), the symptom characteristics (extensive and severe pain poorly responsive to therapy and acute autonomic symptoms), and the concomitant worsening retinopathy [1]. However, our patient has not recovered after 6 years, whereas Gibbons et al. described improvements in most patients after 18 months. The particularly high rate of HbA1c improvement and the impossibility of permissive hyperglycemia, which would have required the discontinuation of immunosuppressive therapy, may have compounded the presumed pathogenic mechanisms, such as endoneurial ischemia, apoptosis, or ectopic firing of regenerating axon sprouts [1]. Our observation is interesting from a pathophysiological point of view, because TIDN occurred without weight loss, exogenous intensive therapy, and hypoglycemic events. A few hours after transplantation, the islet graft function was good enough to rapidly stabilize the glycemia within the normal range, with very low variability and no hypoglycemic events, despite low-dose exogenous insulin. Thus, the relative hypoglycemia due to the rapid improvement in diabetes seems to be the strongest triggering factor, whereas iatrogenic hypoglycemic events or weight loss-induced vitamin deficiency may be aggravating factors.

The question of confounding factors can also be raised, since the patient received immunosuppressive therapy, namely neurotoxic agents. Cartwright et al. reported one case of acute sensory neuropathy occurring during infusion of rabbit-derived antithymocyte globulin in a patient without diabetes [5]. However, that patient showed fever and chills during thymoglobulin infusion, whereas the treatment was well tolerated in our patient, and contrary to our patient, Cartwright's patient recovered within 1 month and did not show any signs of autonomic neuropathy. Tacrolimus has been suspected, but our patient never experienced tacrolimus levels higher than 16 ng/ml at symptom occurrence, which remain unchanged after tacrolimus withdrawal. Besides,

most cases of tacrolimus induced neuropathy presented more frequently with weakness and motor symptoms than acute pain and autonomic dysfunction. Our patient also received a treatment by etanercept, an anti-TNF alpha antibody, in the first 2 weeks after transplantation, but the literature argues for a protective rather than a neurotoxic effect.

TIDN, defined by Gibbons as acute pain or autonomic dysfunction occurring within 8 weeks of a decrease of more than 2% in HbA1c, is not well identified by clinicians and not described after pancreas or islet transplantation. Despite potential confounding factors, our observation seems to be suggestive enough to describe the first case of TIDN occurring after islet transplantation. The rapid glycemic improvement in the post-transplantation period may contribute to increasing the risk of TIDN in patients with HbA1c above 9%, especially if they have preexisting microvascular complications, and raise the question of an upper limit for HbA1c before pancreas or islet transplantation procedures.

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Author contributions LM and SB collected the data and wrote the manuscript. LM, AP, and SB followed the patient. TB contributed to the transplantation procedure. TB, AP, PYB, and SB participated to the TRIMECO Trial inclusion committee.

Compliance with ethical standards

Guarantor's name Sophie Borot takes responsibility for the contents of this article.

Conflict of interest No author has any financial disclosure or conflict of interest related to the content of this article.

Research involving Human participants All procedures performed in the Trimeco study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All human included in the Trimeco trial gave their inform consent prior to the inclusion in the study.

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