Development of type 1 diabetes mellitus in a patient with rheumatoid arthritis receiving anti-tumor necrosis factor alpha

Sirs,

Clinical autoimmune phenomenaon have been reported to occur during TNF blocker therapy (1-3), including type 1 diabetes mellitus (T1DM) (4). T1DM is an autoimmune disease due to immunological reactivity to pancreatic islet cells. Both genetic and environmental factors have been shown to be involved (5). We report the development of T1DM in an adult rheumatoid arthritis (RA) patient during TNF blocker therapy associated with the appearance of anti-glutamic acid decarboxylase (GAD) antibodies, which were not present before treatment.

A 48- year-old woman with a past medical history significant for RA with positive rheumatoid factors was transferred to our unit for TNF blockade therapy. She weighed 94 kilograms, and was 163 centimeters tall. The patient's medications included methotrexate 15 mg/week and prednisone 10mg/day, which was subsequently increased to 20mg/day for 1 month for worsening symptoms. Antinuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) antibodies were normal, as was her fasting plasma glucose (4.8 mmol/l; normal range 3.8-6.1 mmol/l). She had no clinical symptoms of insulin resistance. Adalimumab (40 mg/week) was initiated and over the next 2 months the patient's prednisone dosage was decreased to 10 mg/day. But six months later, she suddenly complained of polyuria and polydipsia and was drinking about 5 liters of water daily. She also progressively lost weight (20 kg in 10 weeks) and had severe asthenia. Clinical examination evidenced muscle loss. She was given 10 mg prednisone per day (stable dosage for 13 weeks). Laboratory examination showed elevated plasma glucose level at 38 mmol/l. Basal serum C-peptide was low (0.5 ng/ml) and did not increase after intravenous administration of 1 mg of glucagon (0.5 ng/ml). Glycosylated hemoglobin (HbA_{1C}) was 15.,6% (normal < 6%). In the search for diabetes-related auto-antibodies, only anti-GAD antibodies were positive (qualitative identification). Anti-thyroglobulin antibodies were 130 IU/ml (normal < 60 IU/ml). ANA were positive (titer 1:500, homogeneous pattern) while anti-dsDNA antibodies were negative. The HLA locus was typed as HLA DR4, 7; DQ2, 3. Insulin therapy by infusion was started, and a few days later, we switched to subcutaneous insulin (3 injections/day). Six months later, clinical examination showed a remission of her arthritis and the presence of normal muscle. HbA_{1C} was decreased (6.3%). The patient's ANA antibodies remained positive (titer 1:500, homogeneous pattern), however her anti-GAD antibodies were negative. Adalimumab was maintained because of the irreversible destruction of the pancreatic islet cells and the efficacy on joint symptoms.

This report describes the development of diabetes mellitus and an euthyroid autoimmune thyroid disease in an adult patient suffering from RA, after administration of a TNF blocker.

Despite the elevated BMI (35 kg/m^2) and the prednisone treatment, the diagnosis of T1DM was established. The sudden onset of the symptoms apparition, the rapid loss of muscle, the loss of insulin secretion (no increase in peptide-C during glucagon test), and the concomitant appearance of anti-GAD antibodies are suggestive of this diagnosis in a predisposed host (HLA DR4).

The association of autoimmune arthritis and endocrine autoimmunity has been previously been described (6), however, in our case, the unusual acute onset of T1DM in an adult patient receiving TNF blocker therapy suggest that TNF blockade may induce this autoimmune disorder. Biological evaluation performed before anti-TNF treatment (until two years before) did not show any changes in glucose levels. After administering the TNF blocker, plasma glucose was still normal. Blood glucose increased only with the first clinical symptoms. Banked sera (collected before administration of adalimumab) were tested for anti-GAD antibodies and were negative, thus pointing to a temporal association between the first diabetic symptoms and the onset of anti-TNF therapy.

TNF could prove beneficial in autoimmunity through immune and disease suppressive activities (7). It was found to protect non-obese diabetic mice from autoimmune diabetes by preventing the development of autoreactive islet-specific T cells (8). Furthermore, it inhibits the release of IFN-α by plasmacytoid dendritic cells (pDCs), and TNF antagonists enhance the production of IFN-α/β by pDCs exposed *in vitro* to viruses (9). This could account for the autoimmune events occurring under TNF-α blockers, as with interferon-alpha (10).

In conclusion, the temporal relationship between T1DM and the initiation of TNF blocker therapy in our patient strongly suggests that this treatment either induced or precipitated the clinical autoimmune disorder. Clinicians should be aware of the possible occurrence of T1DM during anti-TNF therapy in predisposed hosts.

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References

1. CUSH JJ: Unusual toxicities with TNF inhibition: heart failure and drug-induced lupus. *Clin Exp Rheumatol* 2004; 22 (Suppl. 35): S141-7.
2. ATZENI F, TURIEL M, CAPSONI F, DORIA A, MERONI P, SARZI-PUTTINI P: Autoimmunity and Anti-TNF-{alpha} Agents. *Ann N Y Acad Sci* 2005; 1051: 559-69.
3. KODAMA S, DAVIS M, FAUSTMAN DL: The therapeutic potential of tumor necrosis factor for autoimmune disease: a mechanistically based hypothesis. *Cell Mol Life Sci* 2005; 62: 1850-62.
4. BLOOM BJ: Development of diabetes mellitus during etanercept therapy in a child with systemic-onset juvenile rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 2606-8.
5. PUGLIESE A: Genetics of type 1 diabetes. *Endocrinol Metab Clin North Am* 2004; 33: 1-16, vii.
6. ALPIGIANI MG, CERBONI M, BERTINI I *et al.*: Endocrine autoimmunity in young patients with juvenile chronic arthritis. *Clin Exp Rheumatol* 2002; 20: 565-8.
7. KOLLIAS G, KONTOYIANNIS D: Role of TNF/TNFR in autoimmunity: specific TNF receptor blockade may be advantageous to anti-TNF treatments. *Cytokine Growth Factor Rev* 2002; 13: 315-21.
8. SATOH J, SEINO H, ABO T *et al.*: Recombinant human tumor necrosis factor alpha suppresses autoimmune diabetes in nonobese diabetic mice. *J Clin Invest* 1989; 84: 1345-8.
9. BANCHEREAU J, PASCUAL V, PALUCKA AK: Autoimmunity through cytokine-induced dendritic cell activation. *Immunity* 2004; 20: 539-50.
10. FABRIS P, BETTERLE C, FLOREANI A *et al.*: Development of type 1 diabetes mellitus during interferon alfa therapy for chronic HCV hepatitis. *Lancet* 1992; 340: 548.