Clinical manifestation of selective IgA deficiency during anti-TNF-α treatment in a psoriatic arthritis patient: case report

S. Iervolino, M. Lofrano, M.N.D. Di Minno, F. Foglia, R. Scarpa, R. Peluso
Department of Clinical and Experimental Medicine, Rheumatology Research Unit, University Federico II, Naples, Italy

INTRODUCTION

The use of anti-tumor necrosis factor-α (anti-TNF-α) agents represents a therapeutic strategy, alternative to traditional Disease Modifying Antirheumatic Drugs (DMARDs) and is used in the treatment of the most part of inflammatory diseases. Anti-TNF-α agents have an important impact in ameliorating both signs and symptoms of several inflammatory rheumatic diseases, improving patients daily life (1). On the other hand, the cytokine blockade results in a potential increase in susceptibility to infections (1); in fact, a variety of infective diseases, especially granulomatous ones (2), have been reported to be associated with the use of TNF-α blockers. Therapy with TNF-α blockers has been shown to increase this infectious risk as compared with traditional treatments (3). Selective IgA deficiency is the most common primary immune-deficiency. Its incidence ranges from 1:163 to 1:18500, depending on the screened population and on the definition of IgA deficiency applied (4). Although most of the patients are often asymptomatic (85-90% of the cases), IgA deficiency has been associated with a wide range of disorders, such as recurrent infections, autoimmune conditions, and malignancies (4, 5). It usually occurs sporadically, but may also be transmitted as an autosomal dominant or autosomal recessive trait or can have polygenic inheritance. IgA deficiency can also be acquired after congenital viral infections (Epstein-Barr virus, cytomegalovirus, rubella) or exposure to certain drugs (anticonvulsants, anti-inflammatory agents), or consequent to lymphoid system damage (splenectomy, adenoidectomy, tonsillectomy, or bone marrow transplantation) (5, 6). In this report we describe the therapeutic management of a Psoriatic Arthritis (PsA) patient affected by selective deficiency of serum IgA.

CASE REPORT

We describe the case of CZ, a Caucasian 28 year-old male patient for whom PsA (pe-
Clinical manifestation of selective IgA peripheral with axial involvement) was diagnosed when he was 8 years old; he did not respond to traditional therapies. In order to evaluate his eligibility to treatment with anti-TNF-α agents, in July 2008 he was referred to the Regional Reference Center for “Biologic Therapy” of Rheumatic Diseases at University of Naples “Federico II”.

### CLINICAL HISTORY

The patient was a construction worker weighing 71 kg, non-smoker, intolerant to cow’s milk proteins, complaining of alternate bowel constipation and diarrhea. He denied any surgery intervention and significant previous infections, excluding two acute bronchitis episodes in the last two years. First articular manifestations (inflammatory low back pain and swelling to the right knee) had been reported when the subject was eighteen. In that period he was referred to his family doctor who did not diagnose PsA and prescribed only several courses of non-steroid anti-inflammatory drugs (NSAIDs).

Two years later, psoriatic lesions appeared at the periumbilical area, elbows and armpits. A Dermatologist prescribed Cyclosporine A (150 mg/day), resulting in a complete regression of the skin manifestations within 6 months. After this period, Cyclosporine A treatment was withdrawn and NSAIDs courses were prescribed when required. One year later arthritis to the knees occurred and the low back pain worsened again. After consulting a rheumatologist in a Rheumatology Department other from ours, PsA was diagnosed and Sulfasalazine (1,500 mg/die) was prescribed. The treatment was continued for two months and stopped because of gastro-intestinal intolerance (diarrhea and gastric pain), that decreased after drug withdrawal. During a following outward visit, Methotrexate was prescribed (10 mg/week i.m.). This treatment was stopped three months later, because transaminases values were twice as high as the standard levels. Therefore, the patient was treated with NSAIDs whenever required.

He first came to our attention on July 2008, in order to evaluate the possibility of using TNF-α blocking drugs. The clinical history, apparently, did not evidence any contraindication for anti-TNF-α therapy; the results of instrumental and hematological exams, carried out for pre-therapeutic screening, were negative, excluding serum protein electrophoresis (SPEP), revealing a mild reduction of the rate of the β-2 band (2.7%; normal values 3.2-6.5%), a relative increase of albumin band (67.6%; normal values 55.8%-66.1%) and of inflammatory reactants (ESR:44 mm/h; normal value <15 mm/h; CRP: 5.5 mg/dl; normal value <0.5 mg/dl). At physical examination a significant swelling to the right knee, 8 tender joints and low back pain have been found, with diffuse psoriatic skin lesions. The clinimetric evaluations were performed and resulting outcome measures were: BASDAI: 7; BASMI: 8.5; HAQ: 2; VAS-pain: 8; PhGA: 7.

As a consequence, the patient began a treatment with Adalimumab (ADA) (40 mg every two weeks s.c.). In October 2009, 40 days before the planned control, the patient came to our attention because he had a fever (temperature(T)-max 38.5°C), with a mucus-producing cough and sore throat. Moreover, the patient evidenced lesions secondary to Herpes Simplex Labialis (scab stage) infection. These clinical manifestations regressed after antibiotic therapy (Amoxycillin plus Clavulanic Acid, 2 g/die for 7 days) and ADA withdrawal. The clinical outcome indices were: BASDAI 6.7; BASMI 8; HAQ 2; VAS-pain 8; PhGA 7, without significant skin manifestations. Seven days after the admission to the hospital he restarted the standard dose of ADA. In January 2010, he returned earlier than expected because he had another infective recurrence. He exhibited folliculitis on the arms, on the chest and on the upper back, mycosis of the oral cavity with inflammation of the hard palate and the reoccurrence of Herpes Labialis (Fig. 1). He also reported another episode of fever (T-max 38°C), with diarrhea (more than 10 evacuations during the day) and dysuria. Laboratory exams showed an urine-culture
positive for *Enterococcus fecalis*, normal rate of CPR and ESR, relative monocytosis at the blood count, without leucocytosis. No swollen joints were found and the results of the outcome tests were: BASDAI: 4; BASFI: 5.5; HAQ: 1.5; VAS-pain: 6; PhGA: 6. During the previous two weeks, the patient also reported the constant presence of the mucositis and herpes labialis manifestations. Therapy with ADA was withdrawn and administration of antibiotic and antimycotic drugs was started. Then, we evaluated the serum immunoglobulins, complement components C3 and C4, SPEP and the blood count. All values resulted within the normal range, excluding the dosage of serum immunoglobulin showing a significant reduction of IgA levels [IgG: 9.57 g/l (n.v. 7-16 g/l); IgM: 0.843 g/l (n.v. 0.4-2.3 g/l); IgA <0.069 g/l (n.v. 0.7-4 g/l)]. We repeated the serum dosage of immunoglobulins, 7 (T1) and 28 (T2) days after the last administration of ADA, evaluating also the lymphocytic sub-population by flow cytometry technique. These exams confirmed reduced levels of serum IgA - regardless ADA administration times (T1:0.063 g/l; T2:0.063 g/l) - and showed a reduction of the CD3+DR+ lymphocytes sub-populations (antigen presence 7%). This provided the diagnosis of selective deficiency of serum IgA (7). A complete regression of the infective manifestations was obtained about 60 days after the last administration of ADA. We did not reintroduce the anti-TNF-α therapy and the patient was treated with Cyclosporine A (150 mg/day) and low-dosage (4 mg/day) metil-prednisolone with partial clinical response but absence of infective manifestations in the following 6 months.

**DISCUSSION**

Anti-TNF-α therapy is clearly related to an increase of infective diseases incidence. Therefore, it is contraindicated in patients with active infections and should be considered with caution in case of acquired or congenital immunodeficiencies. In this case-report the sub-clinical congenital immunodeficiency became relevant during anti-TNF-α treatment. In fact, IgA deficiency did not determined significant clinical manifestations until the administration of ADA began. In our case, anti-TNF-α therapy increased both the number and the duration of the infections, making the suspension of the administration of ADA necessary. It is worth underlining that serious infections, needing the hospitalization of the patient, did not develop. This was probably due to the strict monitoring exerted and to the specific anti-microbic therapies administered. It is therefore necessary to carefully consider the susceptibility to infections and the real necessity for biological treatment. In our knowledge, little is reported about TNF-α blockers therapy in patients affected by any type of immunodeficiency (7).

It is interesting to note that some data showed that IgA deficiency has been associated with a wide range of disorders, such as autoimmune conditions and malignancies (4, 5). In particular Crohn’s disease, celiac disease, and psoriasis were observed in 20.6% subjects affected by IgA deficiency (8). In our opinion, these data are very important for rheumatologists because these autoimmune conditions are significantly linked to spondyloarthritidies (9, 10). Another reason to carefully study the immune...
status of patients who are candidate to receive anti-TNF-α treatment is the cancer risk. In fact, an association of malignancy (especially hematological and gastrointestinal cancers) with IgA deficiency has been documented (11, 12). Strober and Sneller estimated that the risk of malignancy in patients with IgA deficiency is about double that of the general population (5).

Although the exact relationship between TNF-α and cancer is unclear, we know that anti-TNF-α therapy exerts biologic effects on carcinogenesis and tumor progression, the impact of which is incompletely understood but is presumably different for different types of cancer and for different time points during carcinogenesis (13). Accordingly with this, the consequences of anti-TNF-α treatment on the short-term and long-term occurrence of cancer remain unclear.

Thus, considering that these immunodeficiency conditions are often asymptomatic and that they are associated with some rheumatic diseases currently treated with anti-TNF-α, we suggest to evaluate carefully the immune status of patients in the pretherapeutic screening for TNF-α blocking therapy; particular attention is necessary for patients with an unusual frequency of infections and, after administering TNF-α blocking therapy, in patients with occurrence of many infections. In particular, because of low cost of the tests, it could be useful to perform the serum immunoglobulin dosage in young subjects with referred allergic diseases and/or frequent infections, first of all, those affecting the upper respiratory and the gastrointestinal systems.

**Conflict of interest:** All the authors have nothing to declare.

### REFERENCES


