Biclonal Gammopathy in a Patient taking Efalizumab for the Treatment of Psoriasis

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Abstract

We report a patient who developed biclonal gammopathy of undetermined significance during treatment with efalizumab for psoriasis. This plasma cell disorder was found during the evaluation of the patient's complaint of mild lower extremity paresthesia. The gammopathy spontaneously remitted following cessation of therapy and has not recurred to date. Given the increasing use and development of biological agents for the treatment of psoriasis and other disorders, this finding and the mechanisms by which it may have occurred is of clinical significance.

Keywords: Efalizumab; Biclonal gammopathy; Monoclonal gammopathy of undetermined significance; Soriasis; Biologics

Introduction

In cases of moderate to severe psoriasis that are refractory to other interventions, biological agents may serve as successful treatment options. One such bioengineered protein is efalizumab, which was approved by the FDA for the treatment of moderate to severe plaque psoriasis in 2003. It is a recombinant humanized monoclonal antibody targeted against CD11a, a component of leukocyte function associated antigen-1 (LFA-1) on T cells. LFA-1 plays an important role in T cell activation and migration, and its inhibition suppresses inflammatory responses involved in the pathogenesis of psoriasis [1]. Numerous phase III clinical trials have demonstrated the efficacy of efalizumab. However, the medication was withdrawn from the market in 2009 when it was linked to cases of progressive multifocal leukoencephalopathy (PML) that occurred in patients who had been using the drug for several years [2]. Other known side effects of efalizumab include infection, arthritis, rebound exacerbation of psoriasis, autoimmune hemolytic anemia, and immune-mediated thrombocytopenia [3]. In addition to PML, efalizumab has been associated with Guillain-Barre syndrome, and chronic inflammatory demyelinating polyneuropathy [4]. An association with monoclonal or biclonal gammopathy of undetermined significance (MGUS, BGUS) has been previously described in only one report to date [5]. We describe the case of a patient who developed BGUS during efalizumab treatment for psoriasis, which spontaneously remitted following cessation of the drug.

Case Presentation

A 52 year-old female with psoriasis presented with a 6-month history of paresthesias affecting the first three toes of her lower extremities. Her medical history was significant for hypertension, hypothyroidism, and hyperlipidemia. She reported no new medications in the past year except for efalizumab (50 mg weekly subcutaneous injection), which was started 10 months prior to treat her psoriasis. Family history was significant for multiple sclerosis in her mother. Physical exam revealed numerous erythematous, scaly plaques involving her hands and feet. She displayed decreased sensation to light touch, pin prick, and temperature in her medial three toes, with mild impairment in proprioception. The rest of the exam was normal.

An electromyelogram was performed that could not rule out a small-fiber neuropathy, and the patient was referred to rheumatology after having a positive ANA titer of 1:1280, total globulin 4.9 g/dL (1.5-4.5 g/dL), and total protein 9.0 g/dL (6.0-8.5 g/dL). A serum protein electrophoresis (SPEP) showed a biclonal gammopathy with gamma globulins measuring 2.9 g/dL (0.6-1.6 g/dL), with 2 paraprotein peaks at 0.9 g/dL and 1 g/dL. Corresponding serum immunofixation electrophoresis (IFE) revealed the presence of an IgG kappa and free lambda light chain paraprotein. These electrophoresis studies were performed approximately 8 months after her initial presentation as part of the continuing diagnostic workup. The patient was documented to have a normal SPEP during the initial workup, with a gamma globulin level of 1.5 g/dL (0.6-1.6 g/dL). Additional laboratory findings included: free kappa/lambda ratio: 1.85 (0.26-1.65), beta-2 (β2) microglobulin: 3.26 mg/L ($\leq$ 2.51 mg/L), IgM level: 71 mg/dL (48-271 mg/dL), IgG: 2914 mg/dL (694-1618 mg/dL), and IgA: 228 mg/dL (81-463 mg/dL). Skeletal survey, cytogenetics, and fluorescence-in-situ hybridization (FISH) for myeloma were all negative, and a bone marrow aspiration and biopsy showed minimal plasmacytosis with up to 5% of plasma cells.

The patient was diagnosed with biclonal gammopathy and was followed every 3 months for repeat laboratory work and annual skeletal surveys. Efalizumab was discontinued at the time of diagnosis after 18 months of therapy. The patient was later treated with excimer laser and topical steroids for psoriasis. Her SPEP biclonal spike, IgG levels, β2 microglobulin, and free kappa/lambda ratio gradually normalized within 12 months after stopping efalizumab. The paraprotein on IFE was no longer detectable by 21 months. She did, however, continue to have persistent, unchanged paresthesias in her lower extremities.

Discussion

Monoclonal gammopathy of undetermined significance (MGUS) is the most common plasma cell disorder. It is distinguished from multiple myeloma by a serum monoclonal protein concentration lower than 3.0 g/dL, fewer than 10% plasma cells in the bone marrow, and the absence of hypercalcemia, lytic bone lesions, or renal insufficiency.

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Biclonal gammopathy of unknown significance (BGUS), which is the simultaneous appearance of 2 monoclonal proteins, occurs rarely, with an incidence of about 1% of all gammopathies [6]. Although limited data for BGUS exists in the literature, it appears to behave and is treated similarly to MGUS [7].

While clinically asymptomatic, MGUS is a known precursor of multiple myeloma (MM), primary amyloidosis, and Waldenstrom macroglobulinemia [8]. The prevalence of MGUS increases with age, occurring in 3.2% of subjects ≥ 50 and 5.3% of those ≥ 70 according to a large epidemiological study in Olmsted County, Minnesota [9]. However, reports to date have not determined an excess risk in patients with psoriasis [10,11]. The current standard of care of MGUS is observation without therapy. As this condition is thought to be the first pathogenetic step in the development of MM, patients generally require lifelong annual follow-up to detect malignant transformation. The average rate of progression to MM or a related malignancy is 1% per year [12]. MM is an incurable disease, and the average survival with current treatment is between 3 and 4 years from time of diagnosis.

We describe the development of BGUS in an individual treated with efalizumab. The likelihood that the drug played a role in our patient's gammopathy is supported by the gradual resolution of her abnormal SPEP and IFE studies following its discontinuation, as well as the absence of known risk factors for MGUS or MM. The disappearance of an M-protein without a known cause or intervention is exceedingly rare [8]. In a study by Kyle et al. (1981) spontaneous resolution occurred in only 27 of 1384 patients (2%) diagnosed with MGUS, most of whom had a small initial monoclonal protein size that could not be measured on densitometer tracings [7]. Prignano et al. described the development of either monoclonal or biclonal gammopathy in 12 patients receiving efalizumab treatment which progressively declined following discontinuation of the drug [5]. Only one known study prior to Prignano et al. has demonstrated a potential association between the use of medication and MGUS. In this population-based case control study, the authors found an increased risk of MM in individuals with a history of taking prednisone, insulin, or anti-gout medication [13].

Interestingly, MGUS has been associated with the presence of peripheral neuropathy, with symptoms including foot numbness and paresthesias as experienced by our patient. In addition, individuals may have aching discomfort, gait ataxia, and sensory deficits in touch and vibration [14]. MGUS-related neuropathies occurs more often in association with IgM paraproteins (60%), followed by IgG (30%) and IgA (10%), with increasing levels of detection obtained with IFE [14,15]. In contrast, only several case reports have described an association of efalizumab with polyneuropathy, all of which were inflammatory demyelinating neuropathies [16]. It is unclear whether the paresthesias in our patient were related to her gammopathy, as her symptoms have persisted despite BGUS resolution.

The exact mechanism by which efalizumab may have contributed to the development of BGUS is unknown. While the etiology of both MGUS and MM remain unclear, it has been suggested that environmental factors, genetic changes, and cytokines IL-1, IL-6, and TNF-α may be involved [12]. In addition, increased expression of adhesion molecules such as CD54, CD106, CD49d, and CD11a may play an important role in binding of MM cells to bone marrow stromal cells, promoting IL-6 secretion and proliferation of tumor cells [17]. LFA-1 expressed by MM cells appears to play an important role in disease pathogenesis, and efalizumab binding to the CD11a component of LFA-1 on predisposed B cells may alter cell proliferation, cytokine production, or survival pathways to promote clonal expansion [18].

Efalizumab's immunosuppressant effect may also contribute to the development of MGUS, as reports exist of MGUS developing secondary to immunodeficiency states and immune dysregulation (such as acquired immunodeficiency syndrome or after organ transplantation) that have resolved with immune system recovery [19,20]. It is also possible that detection of efalizumab itself, an IgG1 kappa antibody, or development of a low-titer antibody to efalizumab, may have been detected and contributed to the biclonal gammopathy. However, pharmacokinetic studies indicate that the mean time to eliminate efalizumab after the last steady-state dose is about 25 days making this a less likely etiology [21].

Conclusion

We describe an association between the biological agent efalizumab and MGUS. While efalizumab has already been withdrawn from the market, the exact mechanism between development of gammopathy and this agent is unclear, and this association may have important implications given the use of other biological agents that are currently on the market and in development for the treatment of psoriasis and other connective tissue disorders. It is important for dermatologists to be aware of this potential side effect, especially when using newer biological agents that may target similar pathways.

References

1. Pastore S, Gubinelli E, Leoni L, Raskovic D, Korkina L (2008) Biological drugs targeting the immune response in the therapy of psoriasis. Biologics 2: 687-697.

2. Di Lernia V (2010) Progressive multifocal leukoencephalopathy and antipsoriatic drugs: assessing the risk of immunosuppressive treatments. Int J Dermatol 49: 631-635.

3. Gottlieb AB, Hamilton T, Caro I, Kwon P, Compton PG, et al. (2006) Long-term continuous efalizumab therapy in patients with moderate to severe chronic plaque psoriasis: updated results from an ongoing trial. J Am Acad Dermatol 54: S154-163.

4. Bechtel M, Sanders C, Bechtel A (2009) Neurological complications of biologic therapy in psoriasis: a review. J Clin Aesthet Dermatol 2: 27-32.

5. Prignano F, Pescitelli L, Ricceri F, Ermini A, Lotti T (2010) Development of monoclonal gammopathy in 12 patients receiving efalizumab treatment for chronic plaque psoriasis. J Am Acad Dermatol 63: e84-87.

6. Eisele L, Dürig J, Hüttmann A, Dührsen U, Assert R, et al. (2012) Prevalence and progression of monoclonal gammopathy of undetermined significance and light-chain MGUS in Germany. Ann Hematol 91: 243-248.

7. Kyle RA, Robinson RA, Katzmann JA (1981) The clinical aspects of biclonal gammopathies. Review of 57 cases. Am J Med 71: 999-1008.

8. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, et al. (2002) A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med 346: 564-569.

9. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, et al. (2006) Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med 354: 1362-1369.

10. Bida JP, Kyle RA, Therneau TM, Melton LJ 3rd, Plevak MF, et al. (2009) Disease associations with monoclonal gammopathy of undetermined significance: a population-based study of 17,398 patients. Mayo Clin Proc 84: 685-693.

11. Eder L, Thavaneswaran A, Pereira D, Sussman G, Gladman DD (2012)

Prevalence of monoclonal gammopathy among patients with psoriatic arthritis. J Rheumatol 39: 564-567.

12. Bladé J, Rosiñol L, Cibeira MT, de Larrea CF (2008) Pathogenesis and progression of monoclonal gammopathy of undetermined significance. Leukemia 22: 1651-1657.

13. Landgren O, Zhang Y, Zahm SH, Inskip P, Zheng T, et al. (2006) Risk of multiple myeloma following medication use and medical conditions: a case-control study in Connecticut women. Cancer Epidemiol Biomarkers Prev 15: 2342-2347.

14. Ropper AH, Gorson KC (1998) Neuropathies associated with paraproteinemia. N Engl J Med 338: 1601-1607.

15. Vrethem M, Larsson B, von Schenck H, Ernerudh J (1993) Immunofixation superior to plasma agarose electrophoresis in detecting small M-components in patients with polyneuropathy. J Neurol Sci 120: 93-98.

16. Victor F, Menon K, Latkowski JA, Fernandez-Obregon A, Strober BE (2008) Efalizumab-associated Guillain-Barre syndrome. Arch Dermatol 144: 1396-1397.

17. Hideshima T, Chauhan D, Schlossman R, Richardson P, Anderson KC (2001) The role of tumor necrosis factor alpha in the pathophysiology of human multiple myeloma: therapeutic applications. Oncogene 20: 4519-4527.

18. Schmidmaier R, Mandl-Weber S, Gaul L, Baumann P, Bumeder I, et al. (2007) Inhibition of lymphocyte function associated antigen 1 by LFA878 induces apoptosis in multiple myeloma cells and is associated with downregulation of the focal adhesion kinase/phosphatidylinositol 3 kinase/Akt pathway. Int J Oncol 31: 969-976.

19. Bladé J (2006) Clinical practice. Monoclonal gammopathy of undetermined significance. N Engl J Med 355: 2765-2770.

20. Sorli ML, Gimeno E, Abella E, Besses C, Knobel H (2008) Smoldering myeloma in HIV patient: a complete remission after antiretroviral therapy. Leuk Res 32: 1482-1483.

21. Raptiva (2012) [efalizumab].