

Secukinumab treatment of Parry-Romberg syndrome



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INTRODUCTION

Parry-Romberg syndrome (PRS), or progressive hemifacial atrophy, is a rare disease of usually hemifacial soft tissue atrophy progressing during several years, often associated with extra-soft tissue manifestations, including neurologic with facial pain, headache or seizures, ophthalmologic with enophthalmos or uveitis, and possible rheumatologic, cardiac, or endocrine changes.^{1,2} Etiopathogenesis is largely unknown, but PRS is believed to be a type of localized linear scleroderma.¹ Aesthetic and functional effects with disease progression can greatly affect the patient, so systemic treatment is recommended.^{2,3} Many systemic and immunosuppressive agents have been used, with various success. Little evidence exists regarding the next step in systemic therapy when these medications are unsuccessful or intolerable.

CASE REPORT

A 21-year-old woman with a 4-year history of progressive left-sided facial atrophy, mild left eye ptosis, and frequent left-sided migraines received a diagnosis of PRS when her neurologist referred her to dermatology, believing the migraines to be PRS neurologic manifestations rather than idiopathic. She had no significant medical history but developed body aches, jaw pain, insomnia, and chronic gastrointestinal upset. Results of magnetic resonance imaging scans of her head were unremarkable except for left-sided facial soft tissue loss with mild laryngopharyngeal deviation. No associated ophthalmologic abnormality was noted, but a maxillofacial surgeon advised occlusal splint for jaw pain not affecting mouth opening.

Methotrexate halted disease progression enough that serial autologous fat grafting (lipofilling)

Abbreviations used:

IL: interleukin
PRS: Parry-Romberg syndrome

surgery was arranged for the cosmetic defect, chosen over synthetic fillers because of a better safety profile and decreased resorption risk. After 9 months of therapy at 5 to 20mg weekly, persistent transaminitis led to a liver biopsy demonstrating chronic mild hepatitis precluded continuation of methotrexate. Subsequent disease progression necessitated postponing lipofilling.

Mycophenolate mofetil 1 g twice daily was ineffective and ceased after 10 weeks; the patient received azathioprine 150 mg daily for 3 weeks but was discontinued because of transaminitis; cyclosporine 100 mg twice daily was discontinued after 3 weeks because of intolerable dizziness, nausea, and abdominal pain; and hydroxychloroquine 200 mg daily after 2 weeks for reversible intolerable tinnitus. Oral prednisone 37.5 to 75 mg daily with slow taper was used intermittently for 2 years when commencing and switching treatments, and then continuously for 6 months at up to 25 mg daily. Prednisone slowed disease progression but did not halt it and caused significant weight gain, acanthosis nigricans, and marginal bone density reduction requiring osteoporosis treatment.

At age 24 the patient had no sign of disease cessation. As little evidence of other successful PRS treatments was found, research regarding cytokines believed contributory in systemic and localized scleroderma was evaluated (Fig 1). An immunologist deemed interleukin (IL) 17A inhibitors potentially

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Fig 1. Patient before starting secukinumab.



Fig 2. Patient after 12 months of secukinumab treatment.



Fig 3. Patient after first autologous fat-grafting surgery while receiving secukinumab.

beneficial. Monthly injections of secukinumab at 300 mg were commenced in June 2018 by compassionate supply, initiated with 3 doses of 500 mg daily intravenous methylprednisone. No facial atrophy progression has been noted on follow up examinations and recent magnetic resonance imaging scan showed no deterioration (Fig 2). The patient underwent lipofilling surgery in November 2019 and June 2020 (Fig 3). Her only adverse effects were sinus pain lasting 48 hours postinjection, controlled with analgesia, and episodic candidiasis, prevented with oral fluconazole taken with injections. She underwent lipofilling surgery in November 2019 and June 2020. She still receives 300-mg monthly injections.

DISCUSSION

PRS involves predominantly unilateral skin, subcutaneous tissue, muscle, and at times bony atrophy, often affecting a trigeminal dermatome, with possible associated pigmentary changes and alopecia.³ Atrophy can continue intraorally, affecting dentition and tongue, whereas trunk and limb involvement are rarely reported.^{2,4} Bilateral cases are less common. Onset usually occurs before aged 20 years, more commonly in female individuals, with true incidence unknown. Disease self-stabilization usually occurs within 2 to 10 years, but slow atrophy progression until then causes functional and aesthetic changes that can affect the patient both physically and psychosocially.^{2,4} Greater repercussions can occur with earlier age of onset because of

the effect on facial development.⁴ Extra-soft tissue manifestations include facial pain, headache, seizures, enophthalmos, and uveitis, as well as possible rheumatologic, cardiac, or endocrine changes.^{1,2} Diagnosis is clinical. Imaging with computed tomography and magnetic resonance shows soft tissue loss and may show brain matter changes that are usually ipsilateral, often of white matter, but can be contralateral.² Our patient had the typical unilateral trigeminal PRS presentation with neurologic manifestations of headache in the form of left-sided migraines, facial pain, and insomnia, with only soft tissue magnetic resonance imaging changes.

Etiopathogenesis is largely unknown, but some cases of familial PRS, preceding facial trauma or infection, and concurrent autoimmune conditions suggest that genetic predisposition, infection, trauma, or autoimmunity may play a role.^{2,5} An association with benign tumors, brain stem center

hyperactivity, metabolic disease, channelopathies, or sympathetic dysfunction from cervical sympathetic trunk trophic malformation is hypothesized.^{2,5} Histologic similarities precipitated the controversial suggestion that PRS is part of a spectrum of scleroderma, being a type of linear localized scleroderma (morphea), similar to *en coup de sabre*.^{1,6} *En coup de sabre* and PRS can co-occur, and differential diagnoses include *en coup de sabre*, other types of localized scleroderma, primary hemifacial hypertrophy, Rasmussen encephalitis, Barraquer-Simons syndrome, and congenital hemiatrophy.^{1,2}

Treatment is difficult. Multidisciplinary management is needed, including ophthalmologist, neurologist for pain and seizure management, and orthodontist, oral-maxillofacial surgeon, or plastic surgeon for dentition, bony involvement, and facial deformity repair once disease is quiescent.² In mild defects, synthetic fillers such as hyaluronic acid can be used but require repetitive treatments and risk migration, foreign body reaction, or increased resorption compared with lipofilling.⁴ Serial lipofilling is therefore preferred in mild to moderate defects, and can be used in conjunction with skeletal and soft tissue augmentation in more severe cases.^{2,4} Systemic therapy to halt disease progress earlier is advised.³ Methotrexate, systemic corticosteroids, mycophenolate mofetil, cyclosporine, azathioprine, and hydroxychloroquine have been used, with variable success.^{2,7} Methotrexate was beneficial in our patient but adverse effects required its cessation. No other systemic agents were tolerable or effective, including long-term oral prednisone. We thus examined the literature regarding cytokine involvement in systemic and localized scleroderma.

Adaptive responses with cytokines related to T helper cell types 1, 17, and 2, including IL-1, -2, -4, -6, -17, and -22; tumor necrosis factor α ; and transforming growth factor β have been implicated in the disease process.⁸ In accordance with this evidence, its safety profile, and accessibility, secukinumab was selected. A fully human IgG1- κ monoclonal antibody against IL-17A, secukinumab directly inhibits IL-17A by selectively binding to it, interfering with its interface with IL-17 receptors.^{9,10} It has a good safety and tolerability profile, believed secondary to its lack of interference with other T helper cell type 17 cell functions or direct effect on the T helper cell type 1 pathway.¹⁰ Nonsevere upper respiratory tract infections and candidiasis are the most common adverse effects.¹⁰ It has been well tolerated in our patient.

Although it is possible the high-dose methylprednisone used in our patient with secukinumab initiation induced disease cessation, it seems unlikely. Ongoing disease progression with no sign of cessation occurred despite 3 years of frequent moderate-to-high-dose oral prednisone, including 6 months of continuous prednisone before secukinumab initiation. The 3 subsequent doses of corticosteroid therefore seem unlikely to have provided the sustained cessation in disease progression we have noted in our patient for the last 2 years of secukinumab use. Secukinumab was probably the main contributing treatment to stabilization of our patient's PRS. This suggests IL-17 probably does play a role in PRS.

CONCLUSION

The likelihood that secukinumab successfully halted progression in our PRS patient suggests that IL-17 plays a role in PRS pathogenesis, as it may with scleroderma. Further research is needed regarding PRS pathogenesis and the use of biologics such as secukinumab for PRS because early successful treatment can decrease effects on the patient aesthetically, functionally, and psychosocially. Our case suggests secukinumab could be considered for treating PRS.

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