Improvement of Stewart-Treves angiosarcoma through interleukin 23p19 inhibition

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Key words: angiosarcoma; case report; guselkumab; IL-23p19; Stewart-Treves; treatment.

INTRODUCTION

Stewart-Treves syndrome (STS) is a rare cutaneous angiosarcoma and represents approximately 5% of all angiosarcomas. It develops mostly in patients with chronic lymphedema, usually in post-mastectomy patients with axillary lymphadenectomy, but it may also have other causes.[1] Given the high rate of metastasis and the very poor prognosis associated with STS, rapid diagnosis is important. Only early surgeries with wide margins, which can include amputation or disarticulation, provide higher chances of survival. Chemotherapy and radiotherapy have not been shown to improve mortality rates. Median survival is estimated to be 7 months.[1]

CASE REPORT

We report the case of an 87-year-old White woman presenting with a large erythematous plaque and coalescent, purple, bullous, easy-to-bleed lesions on her left forearm surrounded by satellite hematic blebs (Fig 1, *A*). She had undergone breast surgery with axillar lymph-node dissection for breast cancer 15 years previously and subsequently developed lymphedema of her left arm. Angiosarcoma due to prominent lymphedema was suspected, and incisional biopsy was performed during plastic surgery.

Histology findings were compatible with Stewart-Treves angiosarcoma and showed irregular branched vascular proliferations with atypical endothelial cells, multiple mitoses, and vascular extravasation (Fig 2). Kaposi syndrome was excluded by the absence of human herpesvirus 8.

Abbreviations used:

IL: interleukin
STS: Stewart-Treves syndrome

Due to the advanced regional disease, surgery would have resulted in amputation of her left arm, which was not desirable. Chemotherapy and radiotherapy treatments were discussed but contraindicated due to the patient's general condition. As the currently available therapeutic options were not feasible, we looked for other options. Based on recent literature describing high levels of interleukin (IL) 23 within this type of tumor and the implication of IL-23 in tumor growth through neoangiogenesis,[2] an off-label compassionate use of guselkumab, an anti—IL-23 cytokine antibody, was considered in order to reduce tumor volume. An urgent request was submitted to the hospital ethics committee to authorize the compassionate off-label use of guselkumab, in accordance with the Belgian law.

After authorization from the ethics committee, Tremfya (Janssen Pharmaceuticals) was administered by subcutaneous injection (100 mg) once a month for 3 months. Pronounced clinical improvement was observed. Two months after initiating treatment, the tumor was dryer (Fig 1, *B*). After 3 months, the lesions had substantially decreased in size, and the spot bleeding had disappeared (Fig 1, *C*). The lymphedema of the forearm also decreased. The satellite nodule attached to the lesion

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IRB approval status: We confirm that the patient gave informed consent for the off-label use of guselkumab, in line with the Belgian law on patient rights concerning the risk and the complications of such a treatment and gave her consent for the publication of her case. Grand Hôpital de Charleroi ethics committee authorized the compassionate off-label use of guselkumab, in accordance with the Belgian law (article 107 §3 of the A.R. 14 December 2006 regarding drug products for human and animal use).

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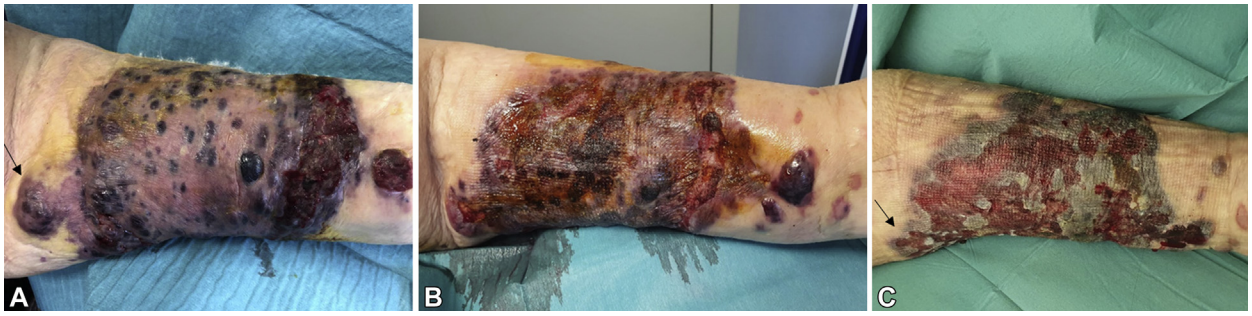

Fig 1. **A**, Clinical presentation of Stewart-Treves syndrome when the patient presented to our Dermatology department before the first guselkumab injection. Erythematous plaque with coalescent, purple, bullous, easy-to-bleed lesions on her left forearm surrounded by satellite hematic blebs (arrow). **B**, Clinical presentation of Stewart-Treves syndrome after 2 months of guselkumab treatment. The lesion was dryer with less bleeding. **C**, Clinical presentation of Stewart-Treves syndrome after 3 months of guselkumab treatment. The lesions had substantially decreased in size, and the spot bleeding had disappeared. The satellite nodule was dryer and smaller (arrow).

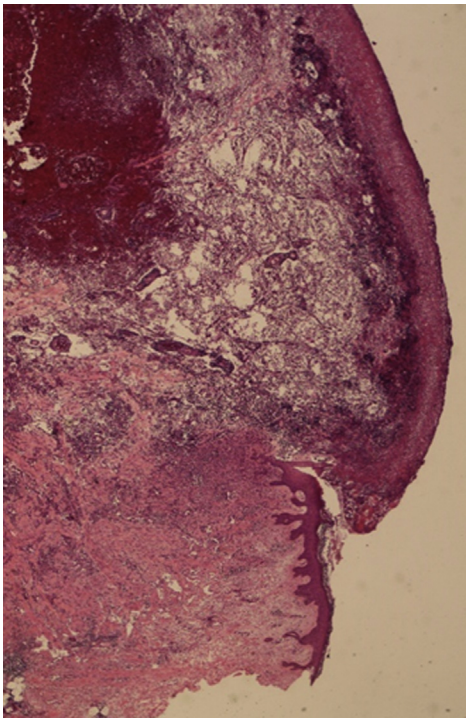

Fig 2. Histopathology findings of Stewart-Treves syndrome. Histologic section shows irregular vascular branching, atypical endothelial cells, multiple mitoses, and extravasation of erythrocytes, compatible with Stewart-Treves syndrome.

regressed considerably (Fig 1, *C*, arrow). The only side effects of the treatment were headache and fatigue lasting a few days following the injections. Anemia during the first month of treatment, due to the constant bleeding of the forearm, required the transfusion of 1 unit of packed red blood cells. With the reduction of the skin lesions, anemia subsequently resolved.

DISCUSSION

To date, the pathogenesis of STS remains unknown. A possible mechanism could be the stimulation of lymph-vessel proliferation in the lymphedematous limb via activation of cytokines, such as vascular endothelial growth factor, following the blockage of the lymphatic vessels. In fact, lymphedema is encountered in most patients who develop STS.[1]

Yoshida et al[2] recently published immunohistochemical analyses of 2 cases of Stewart-Treves angiosarcoma. They employed immunohistochemical staining of IL-23 and IL-17 and detected a significant quantity of IL-23− and IL-17−producing cells at the edge of the tumor.

Immunohistochemical research in skin cancer has shown that IL-23 plays an important role in tumor angiogenesis, via the stimulation of the Th17 pathway and induction of IL-17 production.[3] In addition, Sheng et al[4] highlighted that IL-23 promotes tumor progression via the inhibition of apoptosis. According to Nie et al,[5] IL-23 may play a role in the recruitment of neutrophils and macrophages, leading to cytokine and vascular endothelial growth factor production in the tumor tissue. IL-23 could play one of the most important roles in the pathogenesis of tumors, including skin cancers.

Based on the scientific data discussed above, targeting IL-23 appeared to be a feasible option to reduce tumor volume. Therefore, we proposed guselkumab, a monoclonal antibody targeting IL-23p19, as a treatment option to our patient. Guselkumab is a well-established treatment for psoriasis. Adverse effects are limited and well reported.

Unfortunately, but as anticipated, due to general physical deterioration in this geriatric and oncologic context, our patient died 3 months following her diagnosis. However, guselkumab treatment led to a better quality of life during her last months of life. In this case, guselkumab was administered because no other therapeutic options were feasible. However, given the benefits observed, studies into the effects of guselkumab when given at an earlier stage of STS are warranted.

In conclusion, we report the innovative use of guselkumab injections for the treatment of STS. Other therapeutic options were excluded due to the patient's general condition. Recent data on the implication of IL-23 in STS led us to propose this unconventional treatment to our patient. Within 3 months, pronounced clinical improvement was observed. This case is unusual and further investigations are necessary to prove the efficacy of this IL-23p19 inhibitor in STS. Our case reveals a potential novel therapeutic target for the treatment of Stewart-Treves angiosarcoma.

Conflicts of interest

None disclosed.

REFERENCES

1. Murgia RD, Gross GP. Stewart-Treves Syndrome. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.
2. Yoshida S, Fujimura T, Ohuchi K, et al. IL-23 Expression in Stewart-Treves syndrome: two case reports and immunohistochemical investigation. *Crit Rev Oncog*. 2020;13(1):462-467.
3. Nardinocchi L, Sonego G, Passarelli F, et al. Interleukin-17 and interleukin-22 promote tumor progression in human nonmelanoma skin cancer. *Eur J Immunol*. 2015;45(3):922-931.
4. Sheng S, Zhang J, Ai J, Hao X, Luan R. Aberrant expression of IL-23/IL-23R in patients with breast cancer and its clinical significance. *Mol Med Rep*. 2018;17(3):4639-4644.
5. Nie W, Yu T, Sang Y, Gao X. Tumor-promoting effect of IL-23 in mammary cancer mediated by infiltration of M2 macrophages and neutrophils in tumor microenvironment. *Biochem Biophys Res Commun*. 2017;482(4):1400-1406.