

Comment on “Cutaneous viral infections in patients after kidney transplantation: risk factors”

To the Editor I am writing with regards to the article by Sułowicz et al.¹ I would like to thank the authors for raising the issue of infectious dermatological complications linked to immunosuppressive therapy after solid organ transplantation. The authors investigated the epidemiology of skin viral infections among kidney transplant recipients in great detail. Skin problems, of which skin viral infections are the most common, seriously affect the quality of life of transplant recipients. Skin infection is not only a serious medical problem but also a cosmetic nuisance. In our studies, patients highlighted the cosmetic aspect as one of the most important problems affecting their quality of life.

The study¹ involved a large group of 486 patients of an outpatient clinic at the Department of Nephrology, Jagiellonian University Hospital, Kraków, Poland. They underwent a detailed subjective and physical examination for the presence of any skin lesions and potential risk factors for their development. A viral cutaneous lesion was observed in 189 individuals (38.9%), of which 98.9% were viral warts. Two patients had herpes zoster infection. Cutaneous viral lesions were observed mainly in men, older patients, and with longer follow-up period after transplantation. The most common location of the lesion were the hands and feet. The model of a careful follow-up after diagnosing a skin viral infection, as proposed by the authors,¹ can also be successfully applied in skin cancer (a leading type of neoplasms in recipients).

Another aspect that drew the authors' attention was the effect of the immunosuppressive regimen on the incidence of viral cutaneous lesions. It was proved that individuals treated with cyclosporine A and azathioprine are especially prone to skin viral infection. On the other hand, tacrolimus and mycophenolate mofetil were described to cause those lesions significantly less frequently. The authors used complex and exact statistical methods to describe the data. It will be even more interesting to look at the blood immunosuppressant level rather than at the daily doses.

Another interesting issue is induction therapy with mono- and polyclonal antibodies. In many studies, it seems to be an important risk factor for later viral complications including infection with potentially oncogenic viruses. For this reason, Muromonab-CD3 (Orthoclone OKT3) is no longer used. In my opinion, using T-cell depletion therapy requires the monitoring of the absolute CD3 cell count by flow cytometry. Maintaining the CD3 level between 50 and 80 cells/mm³ could potentially prevent later viral and neoplastic complications. This hypothesis requires more accurate studies in the future. Another interesting finding is that the use of azathioprine was a risk factor of skin viral infection, and the authors' view on this issue would be of particular interest.

Skin lesions after solid organ transplantation are one of the most common side effects of an immunosuppressive therapy. It is of great importance to examine any new lesion because the incidence of skin malignancies is elevated in this population of patients. The authors did not mention whether any of the lesions was neoplastic or whether it progressed to a dysplastic lesion during the follow-up period. This issue seems to be crucial because skin neoplasms in the population of solid organ transplant recipients are particularly malignant. Another aspect that could have been reported in greater detail is the number of skin viral lesions characterized in particular individuals and whether there was any significance between the time after transplantation or immunosuppressive regimen and the number of viral warts. Additionally, viral warts on the hands could have been described more precisely. A number of authors differentiate between the warts on the back of the hands (which are more common) and palms (which are more painful and troublesome).²

In 2003, Schmook et al.³ reported that the adequate treatment for multiple warts caused by human papillomavirus in organ transplant recipients needs to be effective because warts persist over years and the rate of spontaneous remission is extremely low. Moreover, some of these viral warts may present with atypical histological

features and may progress to squamous cell carcinoma.⁴ Shmook et al.³ described the available treatment methods and proposed a promising novel therapy with imiquimod. Sułowicz et al.¹ did not present data on the treatment of viral warts and did not address the issue of whether the treatment was necessary in any individual, what was the treatment administered, if any, and what was its effectiveness.

The final issue that has recently drawn the attention of researchers in many disease states is the quality of life. The authors¹ discussed this in the introduction, but did not report any data. In 2012, Zachariae et al.² published a study on Danish kidney transplant patients, in which they examined the quality of life of individuals suffering from viral warts. They suggested the use of the Dermatology Quality of Life Index.⁵ Sułowicz et al.¹ did not report whether patients with a viral cutaneous infection complained of a decreased quality of life and whether they thus demonstrated a stronger motivation to receive an adequate treatment.

Author name and affiliation Piotr Przybyłowski, Department of Cardiovascular Surgery and Transplantology, Jagiellonian University Medical College, John Paul II Hospital, Kraków, Poland

Corresponding author Piotr Przybyłowski, MD, PhD, Klinika Chirurgii Serca, Naczyń i Transplantologii, Uniwersytet Jagielloński, Collegium Medicum, ul. Prądnicka 80, 31-202 Kraków, Poland, phone: +48-12-614-30-75, fax: +48-12-614-30-72, e-mail: piotr.przybylowski@uj.edu.pl

Conflict of interest The authors declare no conflict of interest.

REFERENCES

- 1 Sułowicz J, Wojas-Pelc A, Kuźniowski M, et al. Cutaneous viral infections in patients after kidney transplantation: risk factors. *Pol Arch Med Wewn.* 2013; 123: 686-692.
- 2 Zachariae C, Sand C, Hansen JM, et al. Warts in a cohort of Danish kidney transplanted patients: impact on quality of life. *Acta Derm Venereol.* 2012; 92: 615-618.
- 3 Shmook T, Nindl I, Ulrich C, et al. Viral warts in organ transplant recipients: new aspects in therapy. *Br J Dermatol.* 2003; 149 (Suppl 66): 20-24.
- 4 Blessing K, McLaren KM, Benton EC, et al. Histopathology of skin lesions in renal allograft recipients – an assessment of viral features and dysplasia. *Histopathology.* 1989; 14: 129-139.
- 5 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. *Clin Exp Dermatol.* 1994; 19: 210-216.

Authors' reply Thank you very much for your interesting comments regarding our article.¹ It should be emphasized that viral infections and skin cancer are a frequent and serious problem in transplant recipients undergoing immunosuppressive therapy. In addition, owing to a continuous increase in the number of transplantations and prolongation of graft survival, we can expect that the population of patients affected by this problem will continue to grow.

As for the potential effect of induction therapy with monoclonal and polyclonal antibodies on the increased incidence of viral infections, it should be noted that induction therapy was not common at the time when most of the analyzed kidney transplantation procedures were performed. In contrast, induction therapy has been recently increasingly used, and, at our institution, it was used in nearly 40% of kidney recipients last year. Of note, in the study group, 6 patients with acute transplant rejection received Muromonab-CD3 (Orthoclone OKT3) and 4 patients received anti-thymocyte globulin (ATG) including 1 treated both with ATG and OKT3. Viral warts were found in 3 patients in this group: 1 patient treated with OKT3, 1 with ATG, and 1 who received both ATG and OKT3. In all those patients, viral warts were located on the hands, and they were numerous (more than 5 lesions) in the patient who received both ATG and OKT3.

It is expected that with the increasing use of induction therapy prior to transplantation procedure, the problem of viral infections and the development of cancer will continue to grow. So we agree with the opinion that further observations are indicated in patients after kidney transplantation who are subjected to many years of immunosuppressive therapy. In the last years, we have observed the development of a treatment strategy, in which azathioprine is being replaced by mycophenolate mofetil and cyclosporine A (CyA) by tacrolimus (TAC). In our unit, the doses of CyA and TAC were adjusted based on their whole blood concentration (TAC, 12.5 ng/ml in the first month and 7.7 ng/ml at 6 months, while CyA [C2 levels] were 1478 ng/ml and 982 ng/ml, respectively).

In the literature, there are reports of a possible malignant transformation of both viral warts and seborrheic keratosis, although it was not observed in our study group. Furthermore, the vast majority of skin tumors observed in our group of patients were located on the face, where the incidence of viral warts is not common. Of the 187 subjects diagnosed with viral warts, multiple lesions (defined as more than 5) were present only in 22 patients and were located mainly on the hands. Unfortunately, we did not analyze the relationship between the number of common warts and the type or time of immunosuppressive therapy. No distinction was made between viral warts located on the back or on the palmar surface of the hands. All patients diagnosed with viral warts due to immunosuppressive therapy received an appropriate treatment. The most common mode of treatment was cryotherapy, which was effective in most patients, especially in those with single warts. Additionally, formulations containing salicylic acid, lactic acid, fluorouracil, and imiquimod were used. Unfortunately, we did not perform any analyses to demonstrate which of the treatment methods was the most effective, and what was the period of

remission of lesions in individual cases. In 3 cases, extensive and treatment-resistant viral warts were observed. One patient underwent therapy with imiquimod but no remission was observed. In the remaining 2 cases, this type of treatment was not possible for economic reasons. The Dermatology Life Quality Index was not measured.

Author names and affiliations Joanna Sułowicz, Anna Wojas-Pelc, Marek Kuźniewski, Ewa Ignacak, Katarzyna Janda, Władysław Sułowicz (J.S., A.W.-P., Department of Dermatology, Jagiellonian University Medical College, Kraków, Poland; M.K., E.I., K.J., W.S.: Department of Nephrology, Jagiellonian University Medical College, Kraków, Poland)

Corresponding author Joanna Sułowicz, MD, PhD, Katedra i Klinika Dermatologii, Uniwersytet Jagielloński, Collegium Medicum, 31-066 Kraków, ul. Skawińska 8, Poland, phone: +48-12-430-52-66, fax: +48-12-430-52-66, e-mail: sulowiczj@interia.pl

Conflict of interest The authors declare no conflict of interest.

REFERENCES

- 1 Sulowicz J, Wojas-Pelc A, Kuźniewski M, et al. Cutaneous viral infections in patients after kidney transplantation: risk factors. *Pol Arch Med Wewn.* 2013; 123: 686-692.