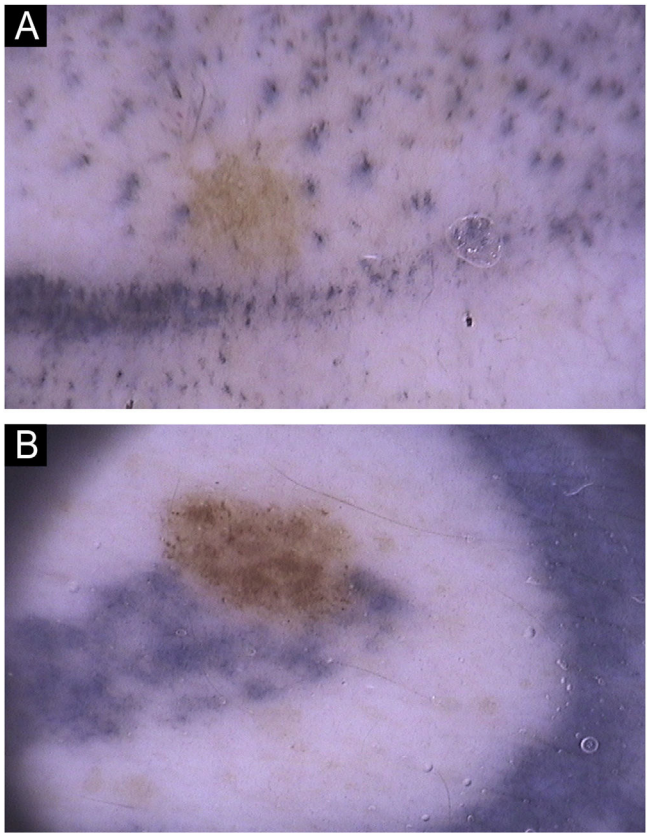

Fig. 4 (A) Perifollicular concentration of tattooing pigment. (B) Nevus causing obliteration of the tattoo; melanin pigmentation extends over the tattoo. Abrupt interruption of the tattooing pigment is observed indicating the possibility of the nevus having appeared after tattooing.

Conflicts of interest

None declared.

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Is arteriovenous fistula a risk factor for squamous cell carcinoma? Evaluation at a University Hospital☆

Dear Editor,

Squamous cell carcinoma (SCC) is the most common neoplasm in transplant (TX) patients, when it is more aggressive and presents a worse prognosis.[1,2] In kidney transplant recipients the occurrence of SCCs is over or close to arteriovenous fistulas (AVF), whether they are active or not. Two mechanisms are proposed: impaired immune response due to overload of the lymphatic system of the affected extremity and, facilitation of HPV-related tumors secondary to surgical trauma due to fistula formation, repetitive punctures, and excision of multiple tumors.[3] Moreover, 3.7%–5% of dialysis patients develop limb ischemia, leading to oxidative stress that can potentiate carcinogenic factors for the development of SCC.[3] After kidney transplantation, many patients remain with an AVF and start using immunosuppressants. These medications add a risk of up to 100× for the development of SCC.[4–6] There is also a greater susceptibility to the HPV virus, with DNA from the virus being found in 80% of SCCs in immunosuppressed patients.[6]

Data from the literature show a high incidence of skin tumors in kidney transplant recipients, but there are no studies that analyze whether the fistula influences tumor development. Therefore, this project aims to report three cases of SCCs appearing close to fistulas, explaining their challenges and analyzing the occurrence of these tumors, whether this association is true or not.

☆ Study conducted at the Universidade Estadual de Campinas, Campinas, SP, Brazil.

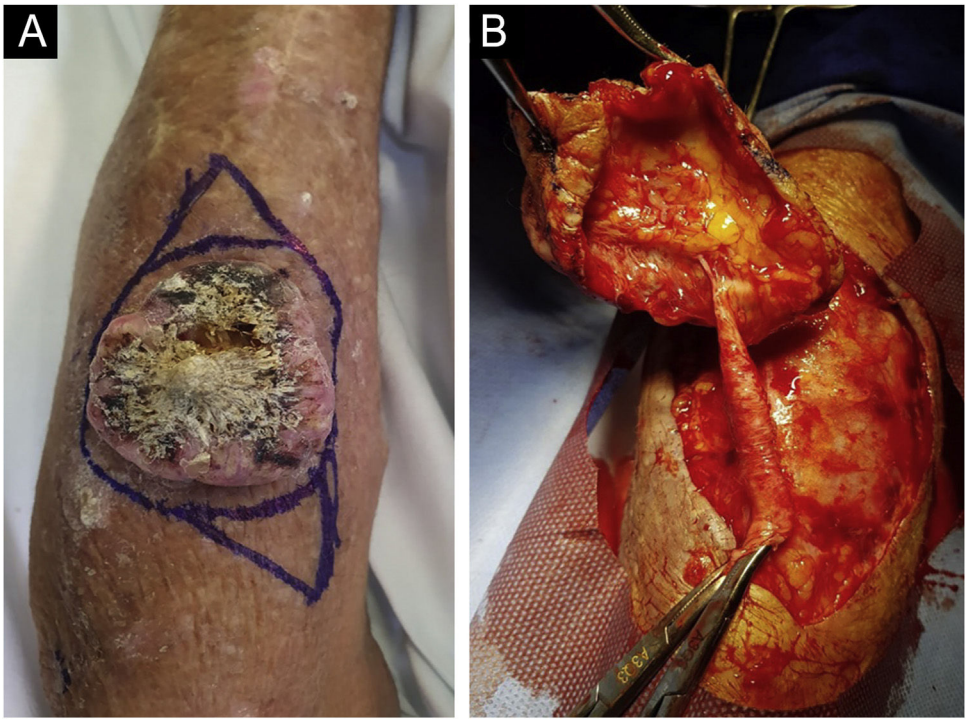

Figure 1 (A) Clinical appearance of the tumor. (B) Intraoperative image showing large vessel entering the excised lesion.

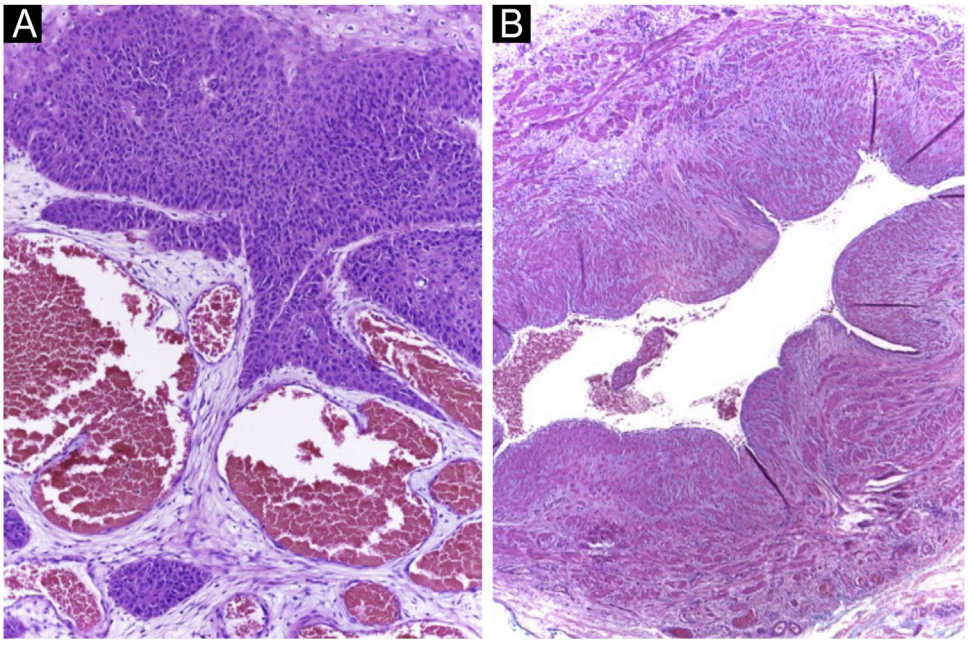

Figure 2 Histopathology of the tumor in Fig. 1 (Hematoxylin & eosin staining). (A) Neoplasm in close contact with vessels derived from the fistula. (B) Disconnected arteriovenous fistula removed surgically.

Materials and methods

Three cases operated at Unicamp Dermatology Service from 2020 to 2022 were selected. A total of 118 patients who had undergone follow-up at the Nephrology and Dermatology Units were also selected to collect data from their medical records, and were divided into groups based on their history of fistula: never had one, inactive or active. In the case of patients with a history of fistula (inactive or active), this upper limb was chosen for analysis, and the upper limb of those who had never had a fistula was chosen at random. A *post-hoc* test was performed to investigate multiple comparisons between fistula history status in the groups. Afterwards, it was decided to group patients with active and

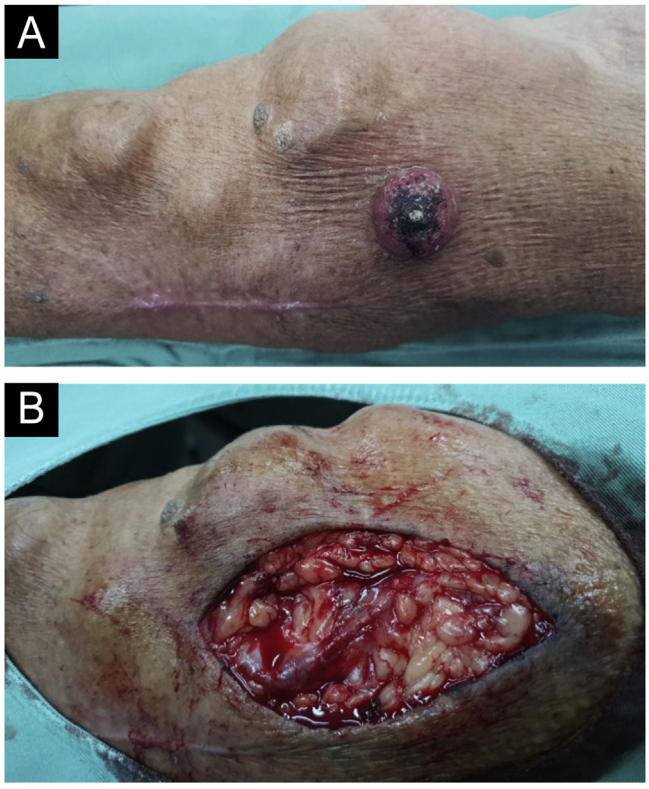

Figure 3 (A) Tumor close to an AVF. Note the scar from a previous excision of SCC. (B) Intraoperative image revealing a medium-sized vessel close to the operated territory.

inactive fistulae and compare them with patients who had never had a fistula using the Mann-Whitney test. All analyses were performed using R software.

Results

Case reports

A 68-year-old male patient, kidney TX recipient (2011), with a 5.0 x 4.0 cm tumor on the left forearm over an inactive AVF. Intraoperatively, an inactive fistula vessel was observed in close contact with the tumor (Figs. 1 and 2).

A 69-year-old male patient, kidney TX recipient (2009), with a 3.5 × 3.0 cm tumor on the left forearm close to an active AVF (Fig. 3).

A 64-year-old kidney TX recipient (2017), with a 1.3 × 1.0 cm tumor on the right forearm, distal to an active AVF (Figs. 4 and 5). High-frequency Doppler Ultrasound was performed (Fig. 4) demonstrating the tumor was 0.6 cm away from the active AVF. The excision was performed after AVF disconnection by the vascular surgery team.

Is a fistula actually a risk factor for SCC?

A total of 118 patients were eligible (25 women and 93 men). Of the total, 80 patients were immunosuppressed (68%) due to kidney, liver, or heart transplantation and 38 were not, and were being followed at the Nephrology department for other kidney diseases. A total of 236 upper limbs were considered, of which 159 had never had a fistula (67%), 43 had an inactive fistula (18.2%) and 34 had an active fistula (14.4%). A total of 164 SCCs were recorded, with an average of 0.69 (minimum zero and maximum 10). Among all SCCs, there was an average of 1.03 in the arms with active fistula; 0.69 with inactive fistula, and 0.62 in those who had never had a fistula.

No statistical significance was found when comparing the occurrence of lesions in the three fistula status groups, (active × inactive p = 0.925; active × never p = 0.0548; inactive × never p = 0.0543).

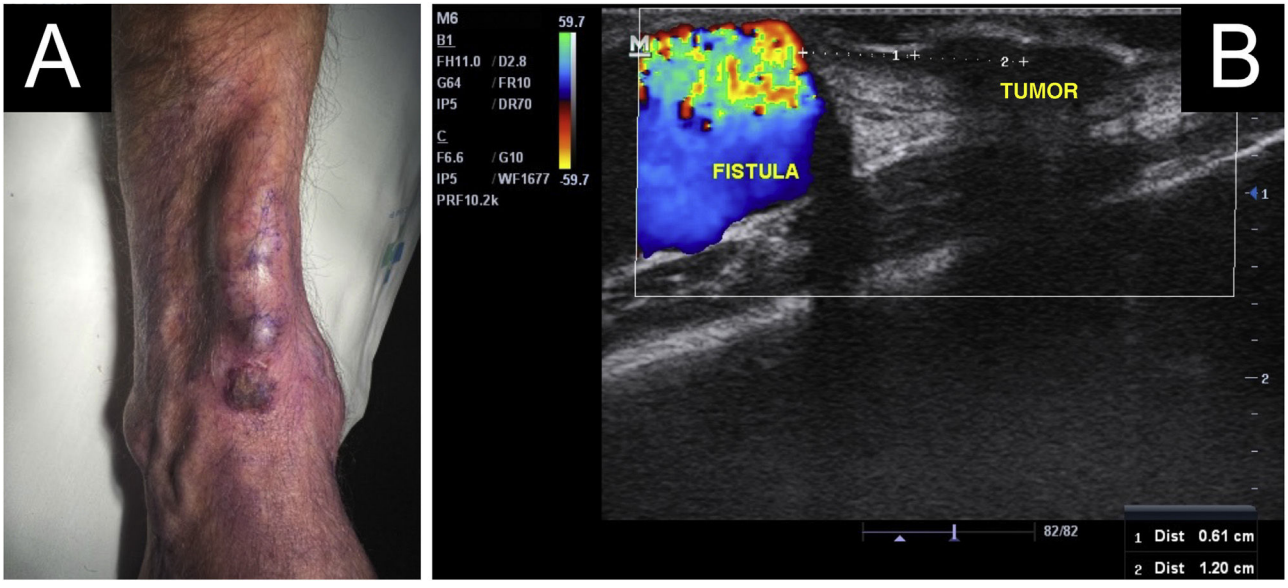

Figure 4 (A) Tumor located distally to an active AVF. (B) Dermatological ultrasound (Mode B and Mindray Doppler, 16 MHz linear probe). Tumor 0.6 cm away from the active fistula.

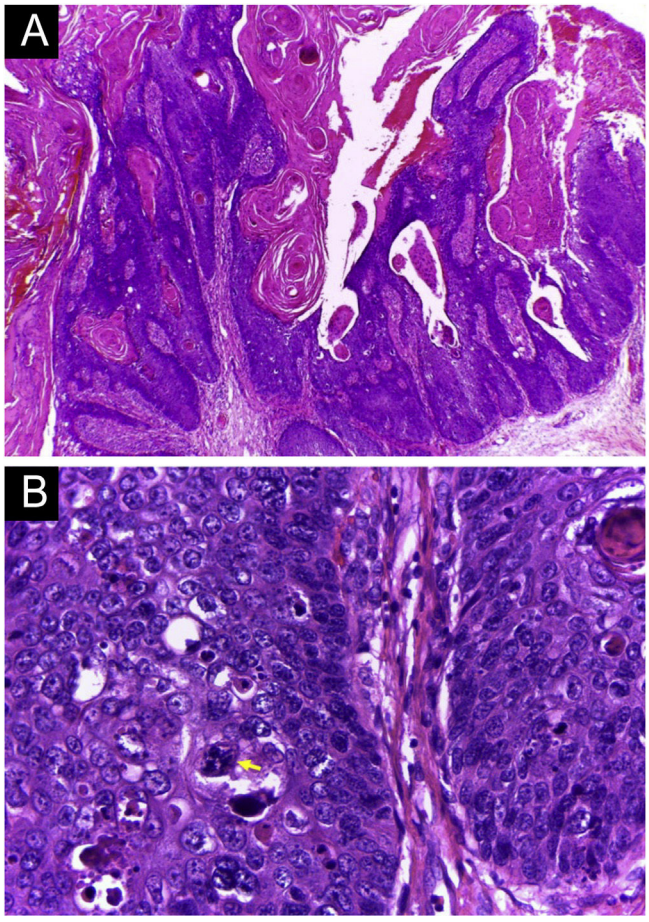

Figure 5 Histopathology of the tumor seen in Fig. 4 (Hematoxylin & eosin staining). (A) Exophytic neoplasm, with papillomatosis and abundant hyperkeratosis, giving it a verrucous appearance (probably due to HPV, secondary to immunosuppression). (B) Atypical hyperchromatic nuclei and an atypical mitoses (yellow arrow).

Considering that having a fistula (active or not) would be the risk factor and that the p-value results from the previous analysis were close to statistical significance, patients with a history of fistula were grouped and compared with those who had never had one, randomizing the choice of one of the arms. Then, statistical significance was found with $p = 0.023$, demonstrating that having a fistula is a risk factor for the occurrence of SCC.

Discussion

The occurrence of SCCs very close to AVFs can be a challenge for treatment by dermatologists, requiring a multidisciplinary approach with vascular surgeons, to disconnect the fistula when authorized by the Nephrology team. Considering the cases followed in outpatient clinic, including those reported in this study, a greater frequency of SCCs was observed in limbs that have or have had an active fistula. The literature had already shown that it could be a risk factor, but there is no statistical evaluation in the literature.

The sample showed that a history of AVF is a risk factor for the development of SCC in the affected limb ($p = 0.023$). Changes in the skin caused by this risk factor, similar to UV exposure, are due to years of dialysis trauma and lymphatic overload, and are not reversible, since even when the fistula no longer functions, the patient still remains at risk of developing SCC in that limb.

This demonstrates the need to pay attention to the formation of tumors in this location, with early treatment of pre-neoplastic and neoplastic lesions, in addition to reinforcing and educating the patient about the need for sunscreen protection.[1]

Conclusion

Immunosuppressed patients require close monitoring due to the high risk of SCCs. Even greater attention should be paid to patients who have had an AVF, whether active or not, since AVFs are a potential risk factor for SCCs.

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Authors' contributions

Ariany Tomaz de Aquino Saran Denofre: Design and planning of the study; data collection, or analysis and interpretation of data; drafting and editing of the manuscript; collection, analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature.

Thais Helena Buffo: Design and planning of the study; critical review of important intellectual content; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; approval of the final version of the manuscript.

Rafael Fantelli Stellini: Collection, analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases.

Maria Leticia Cintra: Collection, analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases.

Renata Ferreira Magalhães: Collection, analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases.

Conflicts of interest

None declared.

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Oral minoxidil 7.5 mg for hair loss increases heart rate with no change in blood pressure in 24 h Holter and 24 h ambulatory blood pressure monitoring☆

Dear Editor,

Low-dose oral minoxidil (LDOM) has emerged as an important alternative for treating different causes of hair loss.[1] Nonetheless, its cardiovascular adverse effects, such as tachycardia, hypotension, and edema, remain a concern even at low doses.

The standard dose for the treatment of hypertension typically ranges from 10 to 40 mg/day, and there is no consensus about the ideal dosage for treating hair loss.[2]

A wide range of doses (from 0.25 to 5 mg/day) has been evaluated in clinical studies, but not exceeding 5 mg/day.[2] Recently, a metanalysis demonstrated a positive dose-dependent association of LDOM with an increase in hair density as well as adverse effects.[2]

We have recently assessed 30 adult males taking 5 mg oral minoxidil for androgenetic alopecia (AGA) with 24-h Holter monitoring and 24-h ambulatory blood pressure monitoring (ABPM) before and after 24 weeks of treatment. They presented no relevant alterations regarding 24-h Holter monitoring and ABPM.[3] These findings were reinforced by an evaluation of 10 men with ABPM at baseline and after the first dose of 5 mg oral minoxidil.[4]

Previous pharmacokinetics studies have shown a mild reduction in blood pressure and a slight increase in heart rate in normotensive patients using oral minoxidil at doses up to 10 mg/day.[5] To assess the potential cardiovascular adverse effects of higher doses of oral minoxidil for hair loss, we increased the dose from 5 to 7.5 mg/day in 11 of the 30 patients who had completed our prior study. After 6-weeks of taking the increased dose, we re-evaluated these patients using 24-h Holter monitoring and ABPM.

The main clinical and demographic data of the participants are presented in Table 1. The ABPM and Holter monitoring results are displayed in Table 2. Despite a subclinical increase in the heart rate, oral 7.5 mg/day minoxidil did not lead to hypotension, tachycardia, or impairment in the nighttime dip.

One participant referred to headache and nine hypertrichoses with oral minoxidil 5 mg/day which did not lead to treatment discontinuation. None of them presented any adverse effects like headache, tachycardia, dizziness, edema, or insomnia after increasing the dose to 7.5 mg/day.

These results reinforce the mild antihypertensive effects of oral minoxidil in normotensive individuals. However, we suggest that doses above 5 mg should not be considered the standard for hair loss treatment and should only be used in exceptional circumstances. In such cases, we recommend that clinicians increase the dose gradually rather than starting with higher doses. It is essential to consider that even very low doses (0.25 mg/day) of oral minoxidil have been associated with uncommon idiosyncratic but severe adverse effects, such as pericardial and pleural effusions.[6]

Table 1 Main clinical and demographic data from the 11 participants of the study.

Variables		Values
Age (years), mean (SD)		37.9 (7.7)
Weight (kg), mean (SD)		86.2 (13.7)
Ethnicity, n (%)	White	8 (73%)
	Brown	2 (18%)
	Black	1 (9%)
Concomitant use drugs, n (%)	Finasteride	2 (18%)

☆ Study conducted at the Clínica Sanabria, Campo Grande, MS, Brazil.