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Diffuse Micro-Nodules on Peritoneal Surfaces at Donor Organ Procurement: Highlights on the Diagnostic Challenge and Transplant Management

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 41-year-old
Final Diagnosis: Diffuse leiomyomatosis
Symptoms: None
Medication: —
Clinical Procedure: —
Specialty: Pathology

Objective: Rare disease

Background: Guidelines have been designed to stratify the risk of cancer transmission in donors with a history of or ongoing malignancy, although this evaluation is not always straightforward when unexpected and rare lesions are found.

Case Report: Here, we present a case of a 41-year-old African female donor who died from a cerebral hemorrhage. Her medical history was unavailable. At procurement, multiple diffuse grayish small nodules were noticed along the peritoneal cavity, some of which were sent to the on-call pathologist for urgent frozen section evaluation. Histology showed a multinodular proliferation of uniform bland-appearing spindle cells, with no evidence of necrosis, nor nuclear atypia or mitoses. The overall picture was consistent with the diagnosis of disseminated peritoneal leiomyomatosis, with overlapping morphology with uterine leiomyoma. Given the rarity of the lesion and the potential for recurrence or malignant degeneration, only the liver and heart were allocated to recipients with life-threatening conditions. The decision was taken in a forcedly limited time and took into account the benefit of transplantation and the risk of disease transmission.

Conclusions: This case highlights challenges that transplant teams often have to deal with, as lesions that are difficult to diagnose during donor assessment are usually not covered in guidelines. The acceptance and usage of organs in such cases has to be decided in a team-based fashion, with the collaboration of all the transplant professionals involved to optimally assess the transmission risk, carefully balancing the benefits of transplantation for the recipients and the need to guarantee a reasonable degree of safety.

Keywords: Leiomyomatosis • Organs at Risk • Transplantation

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Background

The number of patients waiting for a transplant is rising and the availability of donor organs does not meet the needs. For this reason, so-called marginal donors are considered, including those with a history of ongoing malignancy. However, transplantation of an organ from a donor always carries a potential risk of disease transmission [1,2].

Guidelines and recommendations have been published in several countries [3-6] to stratify the risk of cancer transmission of donors with neoplastic potential. Guidelines are mainly based on large registries and sparse case reporting of transmission events, so they cannot cover all the possible findings and situations [7,8]. Indeed, evaluation of deceased donors at procurement can be critical when transplant professionals have to manage cases where an exhaustive medical history is not available or when investigations procedures could not be performed. Even when a reliable diagnosis of unexpected lesions is achieved, its rarity leads often to an uncertain risk assessment of the donor [9]. Our case shows an unexpected finding diagnosed as disseminated peritoneal leiomyomatosis, during the forced limited time of organ procurement, in a donor with no available history. Moreover, the transplant team was obliged to make a critical decision, balancing risks and benefits of using the grafts from a donor with a rare diagnostic entity not covered by guidelines.

Case Report

The organ donor was a 41-year-old African woman who died from a cerebral hemorrhage. A medical history was unavailable and assessment of the donor before organ procurement was performed according to Italian National Guidelines [5]. Blood tests were normal, serology was negative, and all clinical investigations were unremarkable. Ultrasound examination of head and neck and breast did not show any abnormalities, while total body computerized tomography revealed an enlarged, fibromatous uterine corpus. The kidneys, heart, liver, and lungs were allocated to 5 recipients at different transplant centers.

During abdominal exploration at procurement, multiple diffuse grayish small nodules of sub-centimetric size were noticed along the peritoneal cavity, both on the parietal and on the visceral side (**Figure 1**), with extensive involvement of the pre-renal space. The uterus was enlarged due to grayish, fasciculated nodules, the largest measuring 3 cm in diameter. Exploration of the thorax and abdomen ruled out any other sign of malignancy or infection. Some of the peritoneal nodules and the uterus were sent to the on-call pathologist for frozen section evaluation. Histology showed a multinodular proliferation of uniform bland-appearing spindle cells,

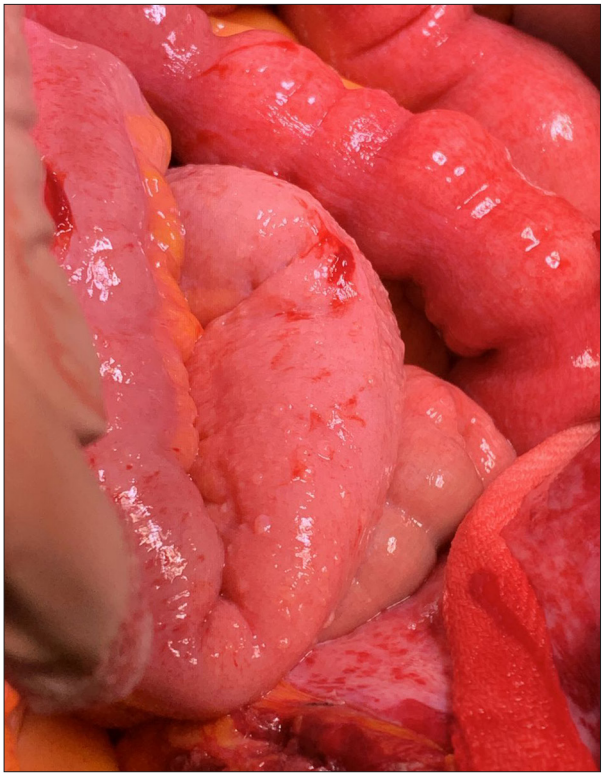

Figure 1. Multiple sub-centimetric grayish nodules on visceral and parietal peritoneum during abdominal evaluation.

with no evidence of necrosis, nor nuclear atypia or mitoses (**Figure 2A, 2B**). Taken together, the clinicopathological findings were suggestive of a mesenchymal proliferation without signs of malignancy, consistent with the diagnosis of disseminated peritoneal leiomyomatosis.

Transplant centers were advised to allocate the organs only to recipients in life-threatening conditions and to implement strict oncological surveillance after transplantation. The heart and liver did not show any alterations and were recovered and transplanted, while the presence of multiple nodules along the course of the ureter and in the pre-renal space precluded use of the kidneys. Immunohistochemistry subsequently performed on the formalin-fixed paraffin-embedded samples confirmed, in the early days after, the diagnosis of disseminated peritoneal leiomyomatosis (**Figure 2C, 2D**). The morphological appearance was indeed overlapping with uterine leiomyoma and no signs of malignancy were found in definitive samples. The recipients underwent a stricter oncological follow-up with more frequent clinical evaluation and imaging if additional elements of suspicion arise. At the time of writing, the recipients are doing well, without signs of disease related to the donor's condition. This study was approved by the Institutional Ethics Committee AOUI Verona (ref. No. 1745CESC).

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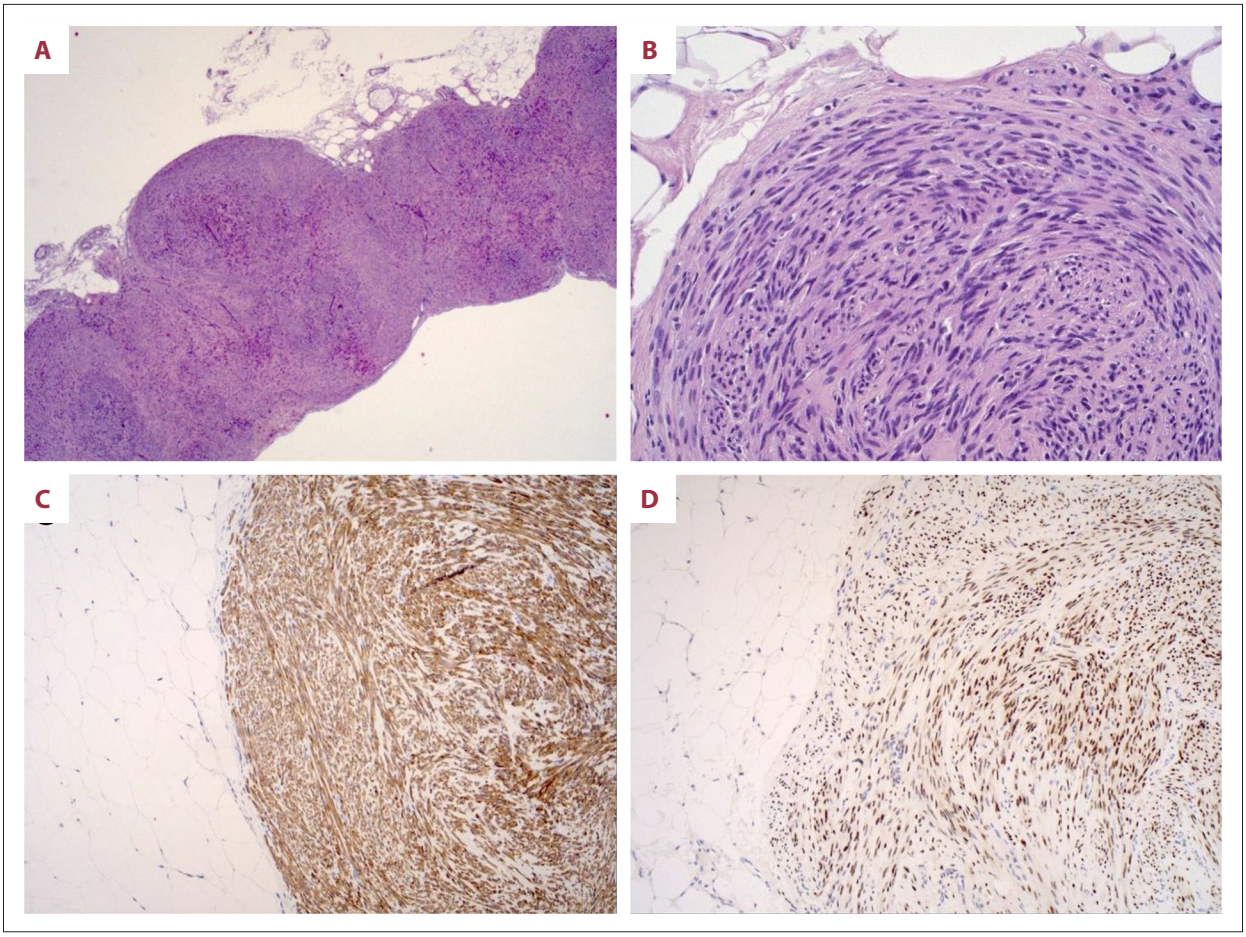

Figure 2. (**A, B**) Histological hematoxylin and eosin staining of a nodule sent to frozen section examination. (**C, D**) At immunohistochemistry, the spindle cell proliferation shows positive phenotype to desmin and smooth muscle actin staining (original magnification: **A:** 2×; **B-D:** 10×).

Discussion

The risk of malignancy transmission with transplant appears to be low according to large series and registries, but it is not zero [10-13]. While guidelines provide a clear indication on managing the organs from a donor with a history of or ongoing malignancy for most cancer types, this is not the case for the rarer and less-described lesions, such as peritoneal leiomyomatosis, whose malignant potential is unclear. Our case is paradigmatic of how an unexpected finding challenged the transplant team in a limited time from the establishment of diagnosis to the definition of the level of risk transmission and therefore the allocation of organs.

First of all, the routine clinical and instrumental investigations performed on the donor did not reveal any relevant abnormality. The small diffuse nodules were discovered during the abdominal exploration, with their number and the spreading appearance on surfaces of peritoneum giving the suspicion of a malignant process. Differential diagnoses comprised a carcinomatous spread of an unknown primary, an infection, or a systemic disease. Histological examination at frozen section showed the features of mesenchymal benign proliferation with spindle cells arranged in whorls and sometimes patternless with no evident cytological atypia, without mitotic figures or evidence of necrosis and hemorrhage. The overall picture of the lesion, together with the presence of a fibromatous uterus, was consistent with a disseminated peritoneal leiomyomatosis, as reported in other cases in the literature [13-15]. Some cases of disseminated peritoneal leiomyomatosis are associated with uterine leiomyomata, as in our case.

Speculations have been made on the possibility of an origin of the lesion after surgical manipulation or interventions for myomectomy [14-17] or caused by a hormonal abnormal estrogenic stimulation causing a subperitoneal mesenchymal stem cell metaplasia [14]. A genetic origin is also hypothesized in association with other diseases, in a model of autosomic dominant disease with incomplete penetrance [18]. Moreover, disseminated peritoneal leiomyomatosis is known to have the

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potential to recur [19,20] and a sarcomatous degeneration has been reported [21,22]. Approximately 150 cases are described in the literature and this is the first case encountered in the setting of limited time of organ donor procurement. The absence of donor history and of comparable managed cases in the literature, together with the rarity and the uncertain malignant potential of this condition, were the main challenges in assessing a correct risk of transmission for the recipients.

Furthermore, in these cases, it is even more important that a reliable diagnosis is provided and that the balance of risks and benefits of usage of the organs is discussed with a multidisciplinary approach, preferably with the consultation of experts in surgical pathology, to better define the level of risk [23,24]. Suitable organs may be erroneously discarded if the nature of the lesion is not reliably assessed, but organs coming from a donor with such a rare lesion should be carefully considered and used with closer follow-up of recipients. The guidelines of the National Transplant Centre and other institutions usually do not cover the specific case, given the rarity and the uncertain malignant potential of these lesions; consequently, the consultation of available experts in the field of pathology and oncology is advisable and should always be part of the decision-making process. Moreover, these decisions have to be made within very strict time constraints of the procurement in order to ensure the correct usage of organs, avoiding their damage or erroneous discard. At the end of the process, it was decided to transplant the organs without changing the recipient allocation, but advising to implement a stricter oncological follow-up in order to provide the benefit of transplantation and at the same time to guarantee the highest possible level of safety. Due to the potential of recurrence and malignant degeneration of disseminated peritoneal leiomyomatosis, transplant centers allocate the organs only to recipients in life-threatening conditions and implement strict oncological surveillance after transplantation. This is stated in the guidelines, but such cases stress once again the importance of transplant team discussion with access to expertise of all professionals involved to keep the opportunity to transplant an organ and the assure the highest possible degree of safety.

Conclusions

The case report reinforces the need for a team-based decision-making, with the participation of all transplant professionals involved, from the procurement surgeons to the pathologists and to the recipients' healthcare providers.

Conflict of Interest

None.

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