

## CASE REPORT

# Uncommon presentation of transitional cell carcinoma: A case report of hand involvement

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**Key Clinical Message**

It is uncommon to see bladder cancer metastases in the hand. A 65-year-old man had bladder cancer surgery 3 years ago. His axilla and wrist swelled after surgery. Final amputation was necessary as the cancer had spread to hand. Transitional cell carcinoma was detected by immunohistochemistry with GATA-3, CK7, CK20, and p63 positivity.

**KEYWORDS**

bladder, cancer, hand, transitional cell carcinoma, urothelial cancer

## 1 | INTRODUCTION

Bladder cancer ranks among the frequently occurring cancers within the urinary system. It constitutes 5% of newly diagnosed cancers in the United States, making it the sixth most prevalent malignant condition.<sup>1,2</sup>

Ureteral neoplasms originate from the urothelial lining of the ureter, which is a component of the urinary system. The most prevalent type of ureteral neoplasm, accounting for approximately 95% of urinary tract malignancies, is transitional cell carcinoma (TCC). TCC can also occur in other regions of the urinary tract, including the renal pelvis, bladder, and urethra. Bladder cancers and those affecting the proximal urethra are classified as lower urinary tract tumors, while neoplasms in the ureter, renal pelvis, and calyces are collectively referred to as upper urinary tract tumors. TCCs demonstrate a high rate of recurrence and can involve any portion of the urothelium, which lines the urinary tract.<sup>3</sup>

TCC is a rare disease that affects the urinary system.<sup>4</sup> About 95% of malignant urinary tumors are TCC.<sup>3</sup>

Smoking is a key factor in the development of TCC. TCC randomly involves any part of the urothelium,

which, depending on the site of involvement, can present with a variety of symptoms, including painful or difficult urination, frequent urination, blood in the urine, and back or abdominal pain.

In a report of 107 patients, the most common site of metastasis of TCC was to the regional lymph nodes (78%). Other common sites included the liver (38%), lung (36%), bone (27%), adrenal gland (21%), and intestine (13%).<sup>2</sup> Many unusual sites of metastatic TCC have also been reported. In the same series, Babaian and colleagues reported metastases to the heart, brain, kidney, spleen, pancreas, meninges, uterus, ovary, prostate, and testes in 1%–8% of their patients.<sup>2</sup> Dhote and colleagues reported metastases in the brain after systemic chemotherapy.<sup>3</sup> Several case reports have demonstrated seeding and implantation of TCC to sites including nephrostomy tracts, laparoscopic and abdominal incisions, the labia minora, and the umbilicus. Other unusual sites include the breast, seminal vesicles, and vas deferens.<sup>5</sup>

The 5-year survival rate of patients with TCC is approximately 77.4%.<sup>6</sup> Several markers, such as GATA-3, P63, CK7, and CK20, can be employed to confirm the diagnosis in cases of TCC.<sup>7</sup> Radiation therapy, chemotherapy,

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and surgery are the available treatments for TCC.<sup>8</sup> We describe a rare case of a large mass in hand, which is a manifestation of TCC in a patient with a history of urothelial cancer. We also review related articles that help to detect rare metastases such as metastasis to the hand in patients with TCC.

A case report by Walsh et al. described the clinical course of a 45-year-old male patient who had been diagnosed with TCC 5 years prior.<sup>9</sup> Initially, the patient presented with metastases to the head and lungs, for which he received chemotherapy. Approximately 2 months later, the patient developed a metastatic lesion in the distal phalanx of the right index finger.

This case report describes the presence of TCC in the hand of a 65-year-old male patient who had been diagnosed with high-grade urothelial carcinoma 2 years prior.<sup>9</sup>

## 2 | CASE HISTORY

A 65-year-old man with a history of high-grade urothelial carcinoma underwent a cystectomy 3 years ago. Two years ago, he experienced swelling in the axillary and wrist regions. A core biopsy revealed metastatic carcinoma with papillary histomorphology, indicating metastatic

papillary urothelial carcinoma. This suggested urothelial metastasis, for which he received chemotherapy and radiotherapy. Following the completion of the treatment period, an FDG-PET scan revealed widespread FDG uptake in the right wrist. After a period of 3 months, specifically on January 10, 2023, a CT scan revealed a destructive mass with erosion in the carpal bones. This mass did not decrease in size compared to the MRI taken a year ago. However, there was a reduction in the size of axillary lymphadenopathy. Additionally, several simple cysts were observed, with the largest one measuring 27 mm in diameter. It is worth noting that the swelling of the hand continued to progress. Two months later, in March 2023, a heterogeneous destructive mass with erosion in carpal bones, which extends from the palmar to the dorsal wrist, was observed again in the CT scan (Figure 1). On August 14, 2023, the hand was amputated and sent to pathology department (Figure 2).

## 3 | METHODS

This case study involved a single patient, a 65-year-old male, with a history of high-grade urothelial carcinoma. The inclusion criteria for this study were patient with a history of high-grade urothelial carcinoma, metastatic

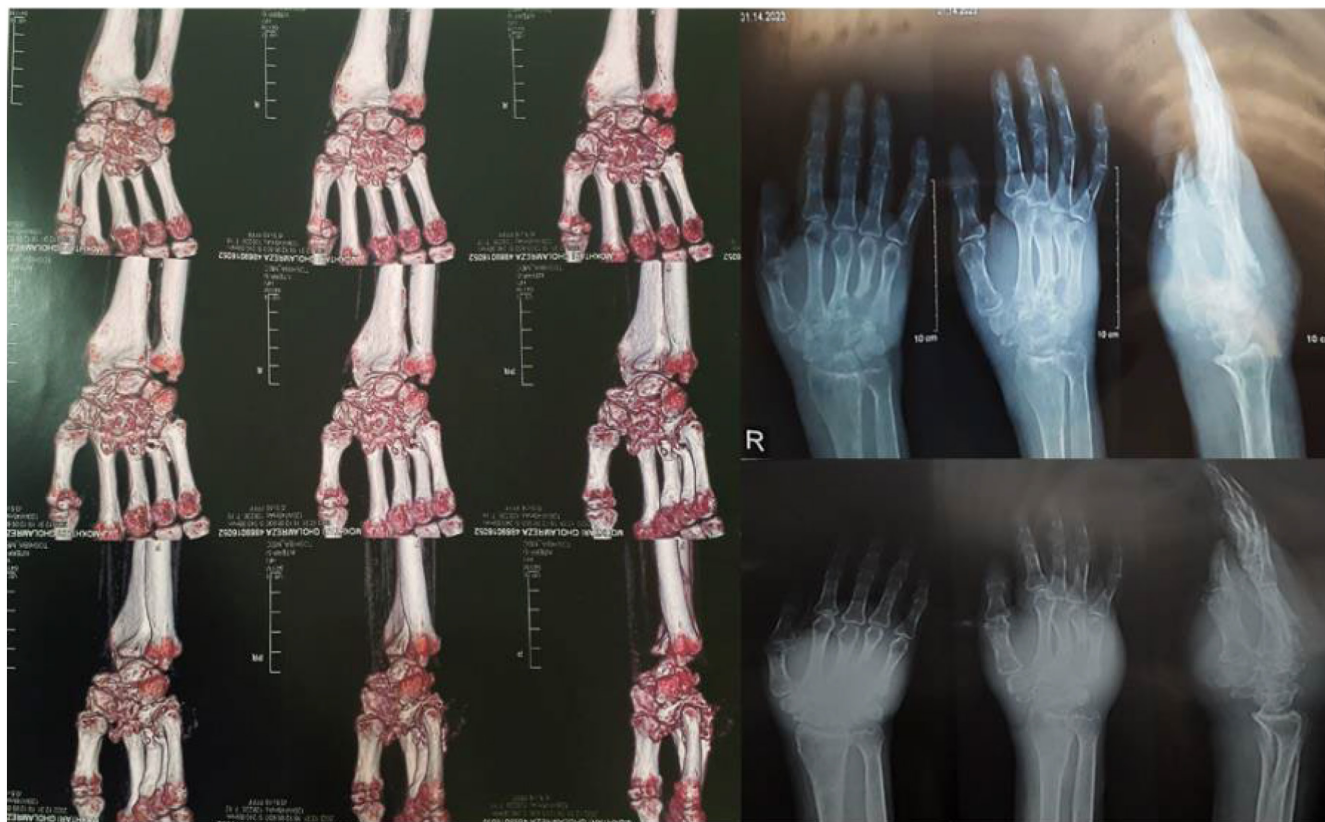
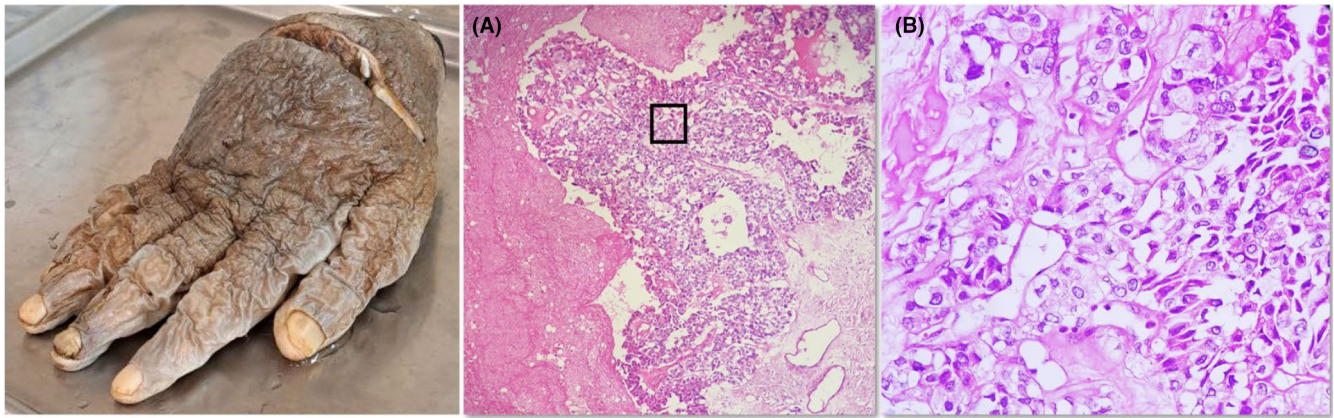


FIGURE 1 A plain radiograph showing the presence of an expansive and lytic lesion in the wrist.



**FIGURE 2** Metastasis of transitional cell carcinoma in the wrist area causes skin tissue destruction and partial scarring. Hematoxylin and eosin (H&E) staining showing complex, and fused papillary structures lined by multilayers of atypical urothelial cells and necrosis (100 $\times$ ) (A), and H&E staining depicting atypical cells with nuclear pleomorphism and nucleomegaly (400 $\times$ ) (B).

papillary urothelial carcinoma, prior treatment with chemotherapy and radiotherapy, metastasis to the hand, lymphadenopathy in the axillary region.

Appropriate ethical considerations were taken, including obtaining the patient's informed consent to participate and utilize their clinical data, maintaining confidentiality of personal information, and ensuring compliance with ethical standards.

In the field of diagnosing bladder cancer metastasis to the hand, the selection of specific antibodies is crucial for accurate diagnosis. GATA-3, a transcription factor, plays a pivotal role in the differentiation of urinary cells and is highly expressed in urinary carcinomas.<sup>10</sup> Cytokeratin 7 is an intermediate filament protein expressed in bladder epithelial cells and is typically found in urinary tract carcinomas, including TCC.<sup>11</sup> Positive staining for GATA-3 and cytokeratin 7 indicates a urinary origin of the tumor.

Cytokeratin 20, similar to cytokeratin 7, is an intermediate chain protein expressed in normal urothelial cells and urothelial carcinoma, suggesting an urothelial origin. Protein p63, a nuclear protein, plays a role in the differentiation of epithelial cells. In urothelial carcinoma, p63 staining can help differentiate between invasive and non-invasive cells.<sup>11,12</sup>

Collectively, these marker panels provide valuable information about the origin, differentiation, and behavior of the tumor, thereby increasing the accuracy of diagnosis.

### 3.1 | Antibodies and other reagents

CK20, CK7, GATA-3, and p63 antibodies were obtained from Abcam (Shanghai, China). Other chemicals were obtained from Sigma-Aldrich (Darmstadt, Germany).

### 3.2 | Histological analysis

The isolated tissue was fixed in paraffin, and 7  $\mu$ m thick layers were cut using a microtome. Hematoxylin and eosin (H&E) staining as well as immunohistochemistry (IHC) were performed according to standard protocols.<sup>13</sup>

In the histological analysis component, the tissue samples were rapidly fixed in 10% formalin to prevent the degradation of antigenic epitopes. The tissues were then dehydrated through a graded series of ethanol solutions and embedded in paraffin. Tissue sections with a thickness of 7  $\mu$ m were prepared using a microtome and mounted on microscope slides. The samples were stained with H&E, wherein the cell nuclei appeared blue-purple, and the cytoplasm and extracellular matrix were stained pink. The stained slides were examined under a light microscope. For the immunohistochemical analysis, the paraffin-embedded samples were first deparaffinized using xylene. Antigen retrieval was performed by incubating the sections in a citrate buffer, and endogenous peroxidase activity was blocked using hydrogen peroxide. Non-specific binding sites were blocked with serum. The tissue sections were then incubated with primary antibodies specific for the following markers: CK20, CK7, GATA-3, and p63. These primary antibodies bound to their respective antigens. A chromogenic substrate, such as 3,3'-diaminobenzidine (DAB), was utilized to visualize the antibody-antigen complexes. Finally, the stained samples were examined under an Olympus CX23 microscope.

## 4 | RESULTS

Histopathological examination and radiographic imaging revealed metastatic TCC in the wrist region, accompanied

by destruction of the adjacent bones (Figure 1). The metastatic involvement of the wrist area resulted in tissue destruction and partial scarring of the skin. The lesion is composed of nests and sheets of cells with papillary pattern, clear cytoplasm, distinct membrane, moderate nuclear atypia with necrosis and scant mitosis (3/10 high power field). Microscopic evaluation of the lesion through H&E staining demonstrated a histological pattern characterized by nests and sheets of cells exhibiting a papillary arrangement, clear cytoplasm, distinct cell membranes, moderate nuclear atypia, necrosis, and low mitotic activity (Figure 2). Abnormal cells with nuclear pleomorphism and nucleomegaly were observed within the lesion. Immunohistochemical analysis was performed to further characterize the neoplastic cells. The markers evaluated included GATA-3, a differentiation marker for urinary cells; CK-7, an epithelial marker expressed in bladder epithelium; CK20, a marker associated with urothelial carcinoma; and p63, a marker of epithelial cell differentiation. The results showed positive staining for these markers, supporting the diagnosis of metastatic TCC (Figures 3 and 4).

## 5 | DISCUSSION

Metastatic involvement of the hand is an uncommon occurrence, which can be easily mistaken for inflammatory conditions, infections, or gout, potentially leading to delays in appropriate treatment.<sup>1</sup> The most common sites of metastasis for TCC are the lung (39.2%) and kidney (10.8%).<sup>14</sup>

TCC typically presents with symptoms such as hematuria (blood in the urine) and urinary incontinence. Risk factors associated with the development of TCC include smoking, exposure to certain chemical agents, and chronic inflammation.

Early detection and accurate diagnosis of TCC are paramount, as immunohistochemical analysis plays a crucial role in confirming the origin of the tumor and guiding subsequent treatment decisions. Among the limitations of the current understanding of TCC metastasis, it is noteworthy that it is a rare occurrence, and the available literature is limited.<sup>15</sup>

Further research is needed to elucidate the underlying molecular mechanisms that contribute to the metastatic spread of TCC.

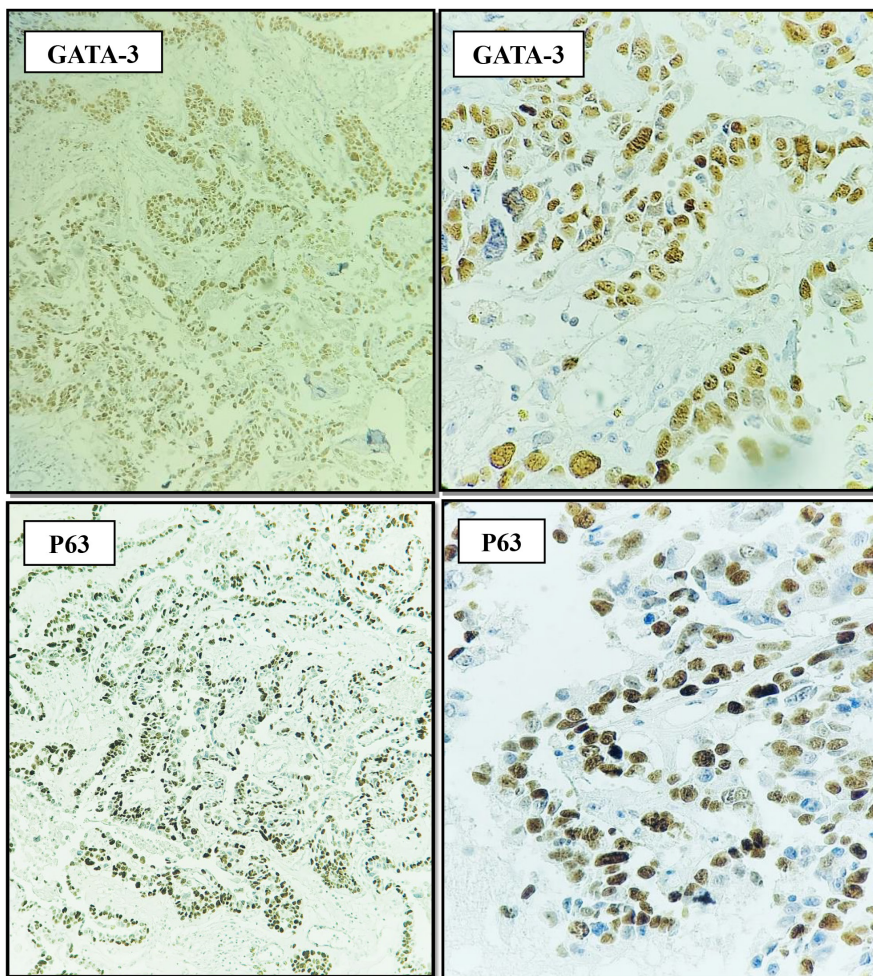
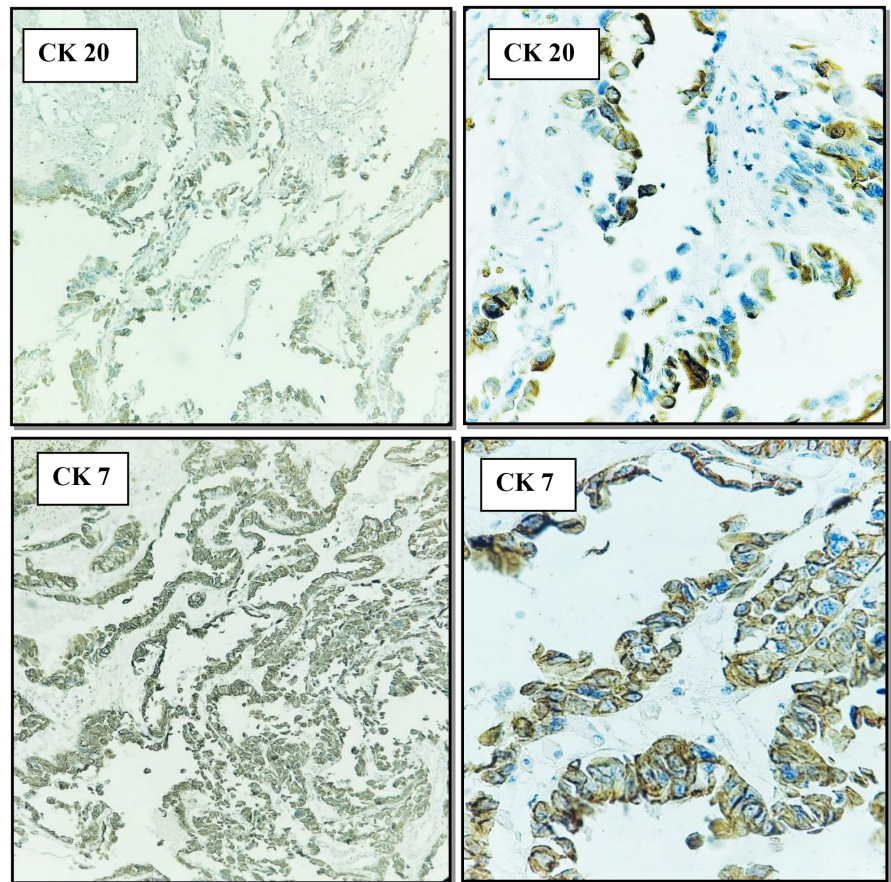


FIGURE 3 Positive IHC staining of GATA-3 and P63 markers (100× and 400×).

**FIGURE 4** Positive IHC staining of CK20 and CK 7 markers (100× and 400×).



Metastasis to the hand most often originates from the lung, breast or kidney, and metastasis from the bladder is very rare.<sup>16</sup> Heymans et al.,<sup>16</sup> Babaian et al.,<sup>17</sup> and Yoneda et al.<sup>18</sup> have reported hand metastases of TCC origin. TCC is a malignant tumor of transitional epithelial tissue origin and is found in the bladder in 90% of cases.<sup>19</sup> In a study, Babaian, et al.<sup>17</sup> observed that the most common site of TCC metastasis was lymph nodes, liver, lung, bone, and adrenal glands. The average age of developing TCC is about 60 years old<sup>20</sup> and the incidence rate in men is 3 times that of women.<sup>21</sup> Smoking is the most important risk factor for TCC.<sup>20</sup> One of the most important symptoms of TCC is hematuria and urinary incontinence.<sup>22</sup> TCC cells are often seen as single cells that invade the lamina propria and muscle layers. They have pleomorphic nuclei, hyperchromasia and high N/C ratio with frequent mitoses.<sup>23</sup> In this study, we observed a case of primary TCC in the axillary and wrist region. In immunohistochemical studies, GATA-3, Cytokeratin 7 (CK7), Cytokeratin 20 (CK20), and p63 markers are used to diagnose TCC and all of them were positive.<sup>24</sup>

GATA-3 is an immunohistochemical marker expressed with high-sensitivity in urothelial cells but not found in other epithelial tumors. The GATA-3 marker has higher sensitivity than uroplakin III and more specificity than P63, S100P, and thrombomodulin. GATA-3 is

characterized by nuclear staining and is a valuable marker in the diagnosis of urothelial cancers.<sup>10,25,26</sup>

The TP63 gene, which belongs to the TP53 tumor suppressor gene family, can produce a minimum of six isoforms as a result of alternate promoter use and alternative splicing. The absence of antibodies specifically targeting individual isoforms of p63 has restricted the examination of the biological importance of p63. The study investigates the expression of p63 isoforms in the urothelium of mice during embryogenesis and in humans during tumor growth. P63 isoforms are expressed by basal and intermediate urothelial cells.<sup>27</sup> P63 is expressed in TCC, while it is not expressed in healthy cells of urothelium and renal cell carcinoma.<sup>28</sup>

CK7 and CK20 are two different types of proteins that are classified as intermediate filament proteins. In most urinary bladder carcinomas, CK7 is expressed. In the normal urothelium of the bladder, CK20 is only seen in the superficial and occasionally intermediate cells of the bladder. An additional diagnostic tool for urinary bladder tumors is the aberrant expression of CK20 in urothelial cancer. CK7 and CK20 are used as markers for the differentiation of urothelial carcinoma and prostatic cancer.<sup>29</sup>

GATA-3 is a transcription factor that plays a crucial role in the differentiation of urinary tract cells. It

is expressed in urothelial carcinomas, and positive immunohistochemical staining for GATA-3 supports the diagnosis of TCC.<sup>10</sup> CK7 is an intermediate filament protein expressed in epithelial cells, including those of the urinary tract. The presence of CK7 expression is commonly observed in urinary carcinomas, and positive CK7 staining indicates a urinary tract origin. CK20 is an intermediate chain protein that is expressed in normal urothelial cells and urothelial carcinomas. The detection of CK20 positivity within a tumor sample suggests a urothelial lineage. p63 is a nuclear protein involved in the development and differentiation of epithelial tissues. In the context of urothelial carcinoma, the expression of p63 can be used to distinguish between invasive tumors and non-invasive lesions.<sup>12</sup>

The findings of the immunohistochemical test demonstrated that our diagnosis was accurate, and metastatic TCC was presented in the hand.

### AUTHOR CONTRIBUTIONS

**zahra sanei-far:** Data curation; methodology.  
**Masoumeh Gharib:** Formal analysis; project administration; writing – original draft.

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### DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

### CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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