—Case Reports—

Early and Post-Treatment Imaging Findings in Perineural Spread: A Pathway to Diffuse Muscle Metastasis in Recurrent Bladder Carcinoma

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Perineural spread (PNS) from pelvic carcinoma has been regarded as a pathway to muscle and bone metastasis. However, few cases have been reported, especially in patients with bladder carcinoma. In the present report, we discuss a case of diffuse cancer involvement in the muscle 5 years after radical cystectomy for advanced bladder carcinoma. Careful observation of temporal changes on medical images confirmed PNS as the pathway to muscle metastasis (i.e., primary PNS). Our report presents early and post-treatment CT, MRI and FDG-PET/CT findings of PNS from the bladder carcinoma.
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Key words: muscle metastasis, bladder carcinoma, perineural spread, PET/CT, MRI

Introduction

Perineural spread (PNS) from pelvic carcinoma has been regarded as a pathway to muscle metastasis[1–3]. It occurs across the neuromuscular junction. However, few cases have been reported, especially in patients with bladder carcinoma. When both PNS and adjacent soft-tissue metastasis coexist, two patterns of invasion has been considered, PNS represents primary (PNS followed by soft-tissue metastasis) or secondary (PNS following soft-tissue metastasis) changes[4,5].

In the present report, we discuss a case of diffuse cancer involvement in the muscle 5 years after radical cystectomy for advanced bladder carcinoma. Careful observation of temporal changes on medical images confirmed PNS as the pathway to muscle metastasis (i.e., primary PNS). Our report presents early and post-treatment imaging findings of PNS from the bladder carcinoma.

Case Report

A 60-year-old man with a history of bladder cancer exhibited diffuse wall infiltration of the tumor at the bladder neck on preoperative imaging. After neoadjuvant chemotherapy, he underwent left nephroureterocystoprostatectomy with pelvic node dissection. The final staging was pT3aN0M0. After three courses of adjuvant chemotherapy with gemcitabine and cisplatin, the patient was considered to have achieved disease-free. Subsequently, we performed CT examination every 3 to 6 months. There was no evidence of recurrence of bladder cancer for 6 years after the operation.

CT examination 5 years after the operation revealed focal swelling of the right obturator nerve without any accompanying findings such as muscle swelling (**Fig. 1a and b**) compared to the images at baseline (**Fig. 1g and h**). At the time of the scan, this subtle change in imaging findings was overlooked. The patient had been aware of right leg pain 4 months after the CT scan. Two months after the onset of leg pain, non-contrast CT revealed diffuse swelling of the right obturator muscle, adductor muscle, and quadriceps femoris muscles (**Fig. 1c and d**).

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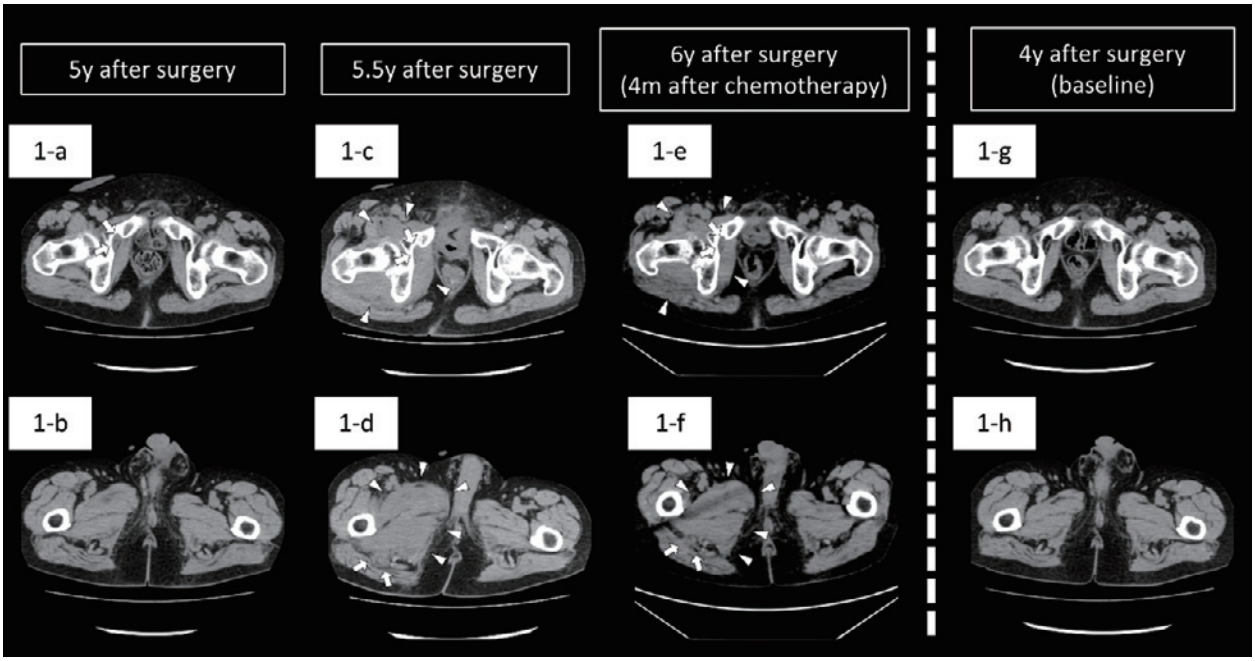

Fig. 1 Non-contrast computed tomography (CT) was performed 5 years after radical cystectomy for advanced bladder carcinoma. CT revealed focal swelling of the right obturator nerve (arrows, a). There were no abnormal findings in the muscle or sciatic nerve (a and b). Four months after the scan and 2 months after the onset of right leg pain, repeat CT was performed. The images show right obturator muscle, adductor muscle, and quadriceps femoris muscle (arrowheads, c and d) involvement accompanying the right obturator nerve and right sciatic nerve swelling (arrows, c and d). Four months after chemotherapy, the muscle swelling had drastically improved (arrowheads, e and f). However, swelling of the right obturator and sciatic nerves persisted (arrows, e and f). For comparison, we also present images obtained 4 years after the initial treatment (g and h). At that time, there was no evidence of any recurrence.

Sciatic nerve swelling was also observed (**Fig. 1d**). Based on these imaging findings, we considered skeletal muscle metastasis in the differential diagnosis. At the time of the scan, creatine kinase (CK) and white blood cell (WBC) count were within normal limits (CK: 147 U/L, WBC: 6,020/μL). For further evaluation, non-contrast MRI and FDG-PET/CT were performed. MRI revealed high signal intensity in the swollen muscles on T2WI and DWI (**Fig. 2 a-d**). Elevated apparent diffusion coefficient (ADC) values may have indicated that the changes were mainly due to vasogenic edema rather than tumor cell infiltration into the muscle (**Fig. 2e and f**). There was no evidence of mass-like lesions or hemorrhage. T2WI also revealed right obturator and sciatic nerve swelling (**Fig. 2 a and b**). On FDG-PET/CT, diffuse FDG accumulation (SUV max: 6.7) was observed, corresponding to areas of high signal intensity on T2WI (**Fig. 3a-c**). Subtle focal uptake of FDG was observed on the distal side of lesions (SUV max: 5.9) (**Fig. 3a**). FDG accumulation in the obturator and sciatic nerves was non-specific (**Fig. 3b and c**). Based on PET/CT findings and palpation, we performed biopsy from two sites in the swollen muscles with particularly high FDG accumulation: the adductor muscle and semimembranosus. Atypical discohesive cells with hyperchromatic nuclei and scant cytoplasm infiltrating between muscle fibers were observed in the adductor muscle sample (**Fig. 4**). Immunostaining was positive for cytokeratin7, cytokeratin20, and p53. These pathological findings confirmed the recurrence of bladder cancer. After 4 months of chemotherapy with gemcitabine and cisplatin, near-complete metabolic responses were observed in the muscle and right obturator and sciatic nerves (**Fig. 3d and e**), although morphological swelling was persistent in the nerves (**Fig. 1e and f**).

Discussion

Recently, PNS from pelvic carcinoma have been investigated mainly from a group of researchers at the Mayo Clinic[1–3,6–9]. They reviewed 17 cases of PNS, including three bladder cases[3]. Among these three cases, two presented with sciatic nerve involvement without solid organ metastasis, while the other presented with both sciatic and obturator nerve involvement accompanied by bone and muscle metastasis[2,6]. The authors provided the following explanation regarding the mechanism underlying these changes[6]. There are two types of nerve plexus

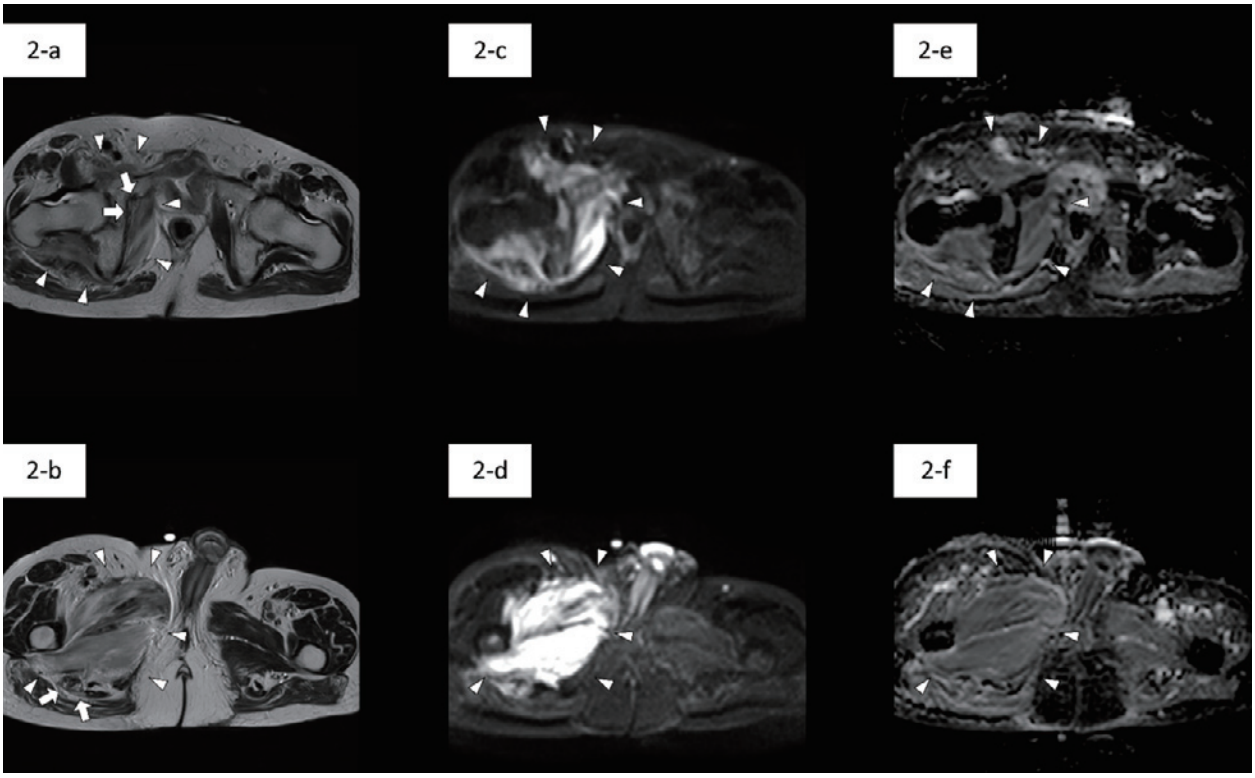

Fig. 2 Magnetic resonance imaging (MRI) was performed 5 years after the initial treatment and 2 months after the onset of right leg pain. T2-weighted imaging (T2WI) shows diffuse swelling of the right obturator muscle and adductor muscle with high signal intensity (arrowheads, a and b) accompanying the right obturator and sciatic nerve swelling (arrows, a and b). The laterality of muscle involvement corresponding to nerve invasion is one of the key appearances of perineural spreading. High signal intensity was observed on diffusion-weighted imaging (DWI) (arrowheads, c and d), with an elevated apparent diffusion coefficient value (arrowheads, e and f).

around the bladder. One is located around the dome and right lateral walls of the bladder. In this region, the bladder receives predominantly parasympathetic innervation derived from the S2-S4 spinal nerves via the pelvic splanchnic nerves. The other is located around the trigone of the bladder. In this region, the innervation by the lowest thoracic sympathetic and lumbar splanchnic nerves via the hypogastric nerves is dominant. In the current case, the primary tumor was located around the neck of the bladder. From this region, the tumor cell was hypothesized to have infiltrated the lumbar plexus via the hypogastric nerve, following which distal spread from the lumbar plexus to the obturator nerve may have occurred. These changes are represented as focal swelling of the nerve, which may be an early imaging sign of PNS. After spread, the tumor distally infiltrated the sciatic nerve via the lumbosacral trunk. Finally, diffuse muscle metastasis occurred via perineurally disseminated cancer. This pattern of PNS is considered "primary" spread. In addition, the Mayo group proposes a "secondary" PNS theory[5]. Secondary PNS occurs when there is a hematogenous and/or lymphogenous metastasis in organs adjacent to the nerve (e.g., muscle, lymph node), followed by PNS from these organs. Nagao et al.[4] presented a case of coexisting PNS and diffuse metastatic muscle infiltration that was very similar to our case. They concluded that PNS was a secondary change. Generally, it is difficult to distinguish between these two pathways when PNS coexists with adjacent organ metastasis.

Imaging of PNS in lumbosacral nerves can be summarized as follows[3]. MRI is the first modality in which subtle changes associated with this disease can be detected. However, in clinical settings, there is no indication for MRI in routine follow-up after tumor resection. As in the current case, incidental PNS can only be detected on CT images. From a morphological perspective, the affected nerves are typically enlarged, often with irregular nodular contours. T2WI shows hyperintensity of PNS as a general finding of tumor infiltration. Notably, secondary changes such as edema of the nerve can also cause the same signal changes on T2WI, which can result in overestimation of the tumor extent. PET can also be used to capture metabolic activity associated with tumor infiltra-

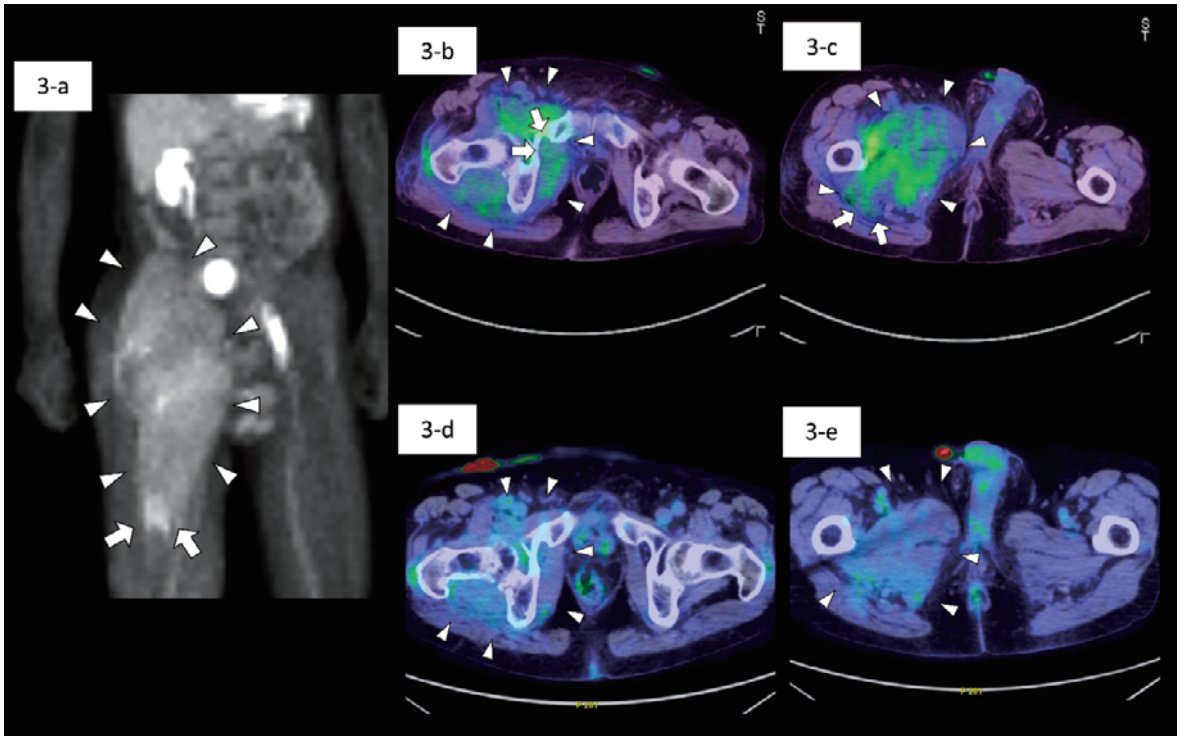

Fig. 3 Fused FDG-PET/CT images show diffuse accumulation of tracer uptake corresponding to areas of muscle swelling (arrowheads, a-c). Subtle focal and skipped uptake was observed on the distal side of the diseases, which was determined as the target of biopsy (arrows, a). FDG accumulation in the sciatic and obturator nerves was non-specific (arrows, b and c). Four months after chemotherapy, tracer accumulation drastically decreased, indicating metabolic remission of the tumor (arrowheads, d and e). FDG: fluorodeoxyglucose; PET: positron emission tomography; CT: computed tomography

tion. In the head and neck region-in which PNS most commonly occurs-FDG-PET has high diagnostic accuracy for the detection of PNS[10]. The utility of this modality in pelvic regions, especially in transitional cell carcinoma, has been reported only in case series[3,7]. In the current case, we observed non-specific accumulation in PNS regions despite clear tumor infiltration of the nerve on CT and MRI. In the current case, an elevated ADC value was observed. This finding is generally considered to reflect vasogenic edema rather than tumor infiltration[11]. There are two possible explanations for an elevated ADC value. In one scenario, a low concentration of tumor cells can result in non-restricted water diffusivity. This type of tumor infiltration was verified in our pathological examination. Alternatively, there may be denervation accompanying PNS in the muscle, representing nonspecific muscular edema[6]. To our knowledge, post-treatment changes in PNS from pelvic carcinoma have not been well documented. In the current case, swelling of the nerve persisted despite a near-complete metabolic response.

Another interesting point of the current case is the rarity with which diffuse muscle metastasis from bladder carcinoma is observed. Muscle metastasis is very rare because of multiple protective factors including muscle pH, muscle contractility, alterations in oxygenation, and lactic acid accumulation[12]. Specifically, muscle metastasis is considered very rare in patients with bladder carcinoma, with fewer than 20 cases having been reported in the English literature[13]. The typical imaging features included focal swelling or ring-enhancement on contrast-enhanced CT. The patients had persistent, localized pain with or without accompanying swelling, and their mean overall duration of survival was 8 months (range: 6-12 months)[14]. Among previous reports, only one case report by Nagao et al.[4] described a patient with diffuse muscle metastasis accompanied by PNS. This type of metastasis may be associated with PNS in patients with bladder carcinoma.

Conclusion

We presented primary perineural spread which is the pathway to the diffuse metastatic muscle infiltration from bladder carcinoma. The focal swelling of the obturator nerve might be an early sign of perineural spread which later invoked diffuse metastatic muscle infiltration. In the current case, there was non-specific tracer-uptake in the nerve involvement on FDG-PET/CT. After the treatment,

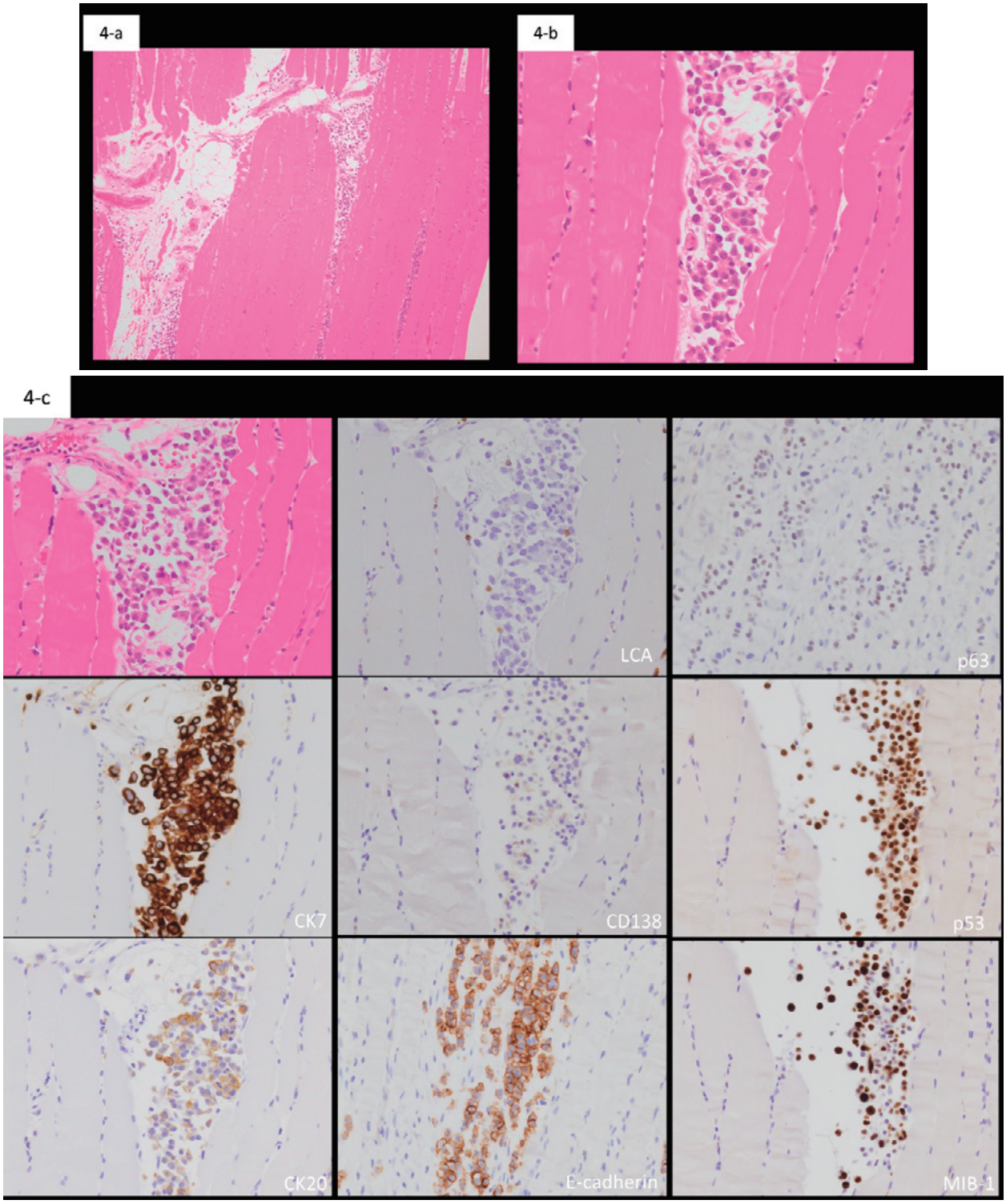

Fig. 4 On lower magnification images of the biopsy specimen (a), atypical discohesive cells with a high N/C ratio infiltrated between muscle fibers, mimicking hematological tumor infiltration. On high magnification images (b), the tumor cells exhibited hyperchromatic round nuclei and scant cytoplasm with loose cell adhesion, which are not typical features of urothelial carcinoma. However, immunohistochemical analysis confirmed that the tumor cells maintained urothelial differentiation, similar to the primary tumor (c).

the nerve swelling was persistent despite almost complete remission.

Conflict of Interest: None.

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