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Bone Vol. 25, No. 2, Supplement
August 1999:85S–90S

Pathology Findings With Acrylic Implants

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We report the pathological findings in cases of acrylic implants obtained by direct intratumoral injection of poly-methyl-methacrylate (PMMA) and *N*-butyl-cyano-acrylate (NBCA). Direct intratumoral injection of acrylic implants was performed for a variety of primary and secondary bone lesions. These types of treatments have been used at our institution in the last 4 years for 40 vertebroplasty (PMMA) procedures and for nine bone lesions of other locations (PMMA, NBCA). Postmortem histology became available for 1 case of PMMA and for 5 cases with NBCA intratumoral acrylic implants. The pathological findings associated with PMMA and NBCA were evaluated and compared. PMMA exhibited a macroscopic and microscopic rim of tumor necrosis, 6 months after implantation. NBCA exhibited compressive effects on the nearby tumor tissue, however, without signs of significant necrosis outside the acrylic tumor cast. Tumor captured inside the acrylic cast showed extensive to near complete necrosis. Acrylic implants may lead to necrosis when injected directly in tumors. The necrotizing effect may extend beyond the limits of an implant in the case of PMMA. Such an extended effect of PMMA, when compared with NBCA, may be due to the variable toxicity of acrylic implants, including the different degrees of the exothermic reaction during polymerization. (Bone 25:85S–90S; 1999)

Key Words: Histology; NBCA; PMMA; Vertebroplasty.

Introduction

Acrylic implants have been used in orthopedic surgery and percutaneous minimally invasive radiological procedures for many years. The use of polymeric implants injected as monomers, and polymerizing within the human body, has been associated with exothermic reactions and toxic effects, mostly attributed to monomeric implant residues.[11,17]

Percutaneous vertebroplasty was introduced a decade ago in France.[9] Although, no randomized clinical studies for the evaluation of the vertebroplasty procedure using poly-methyl-methacrylate (PMMA) as an implant have been published to this date, this procedure has found increasing acceptance. Vertebroplasty has a rate of 80%–90% successful and lasting pain relief in a variety of lesions.[1,4–7,9,12] The lesions of the vertebral body currently addressed include vertebral hemangiomas, vertebral metastatic disease, vertebral osteoporotic collapse, and other less frequent pathologies such as vertebral myeloma.[1,5]

Pain relief is considered to be related mostly to the stabilization of the vertebral body with regard to compressive forces, but also related to the induction of tumor necrosis, and to the destruction of sensitive nerve endings.[8,20] The two latter effects were attributed to the heat liberated during the highly exothermic reaction of the PMMA polymerization.

In follow-up studies of patients treated by PMMA vertebroplasty for metastastic lesions, it is the other secondary tumoral lesions located elsewhere, rather than the previously treated site, that are typically seen to proliferate. These observations were interpreted as the existence of an antitumoral effect induced by the PMMA implant. A similar antitumoral effect of vertebroplasty was reported with the regression of systemic symptoms previously observed in a case of pheochromocytoma.[20]

The antitumoral effect of PMMA was attributed to a variety of causes, including direct heat necrosis during its exothermic polymerization and cytotoxicity. Cytotoxic effect of high doses of methyl methacrylate on rapidly proliferating cells had been demonstrated early in in vitro studies.[15] Toxicity of acrylics, which polymerize inside the human body, may also be related to the presence of residual monomers.[17]

Heat effects have been described related to degree and duration of the heat exposure[11] and the size of the implant.[13] Accordingly, other studies using smaller amounts of implant failed to demonstrate immediate local side effects on adjacent normal bone tissue at the bone-cement interface after total hip replacement in sheep.[14]

The use of other acrylics, such as *N*-butyl-cyano-acrylate (NBCA), has been reported mostly in cases of endovascular treatment of arteriovenous malformations.[17,18] Similar to the direct percutaneous access to bone tumors introduced with the vertebroplasty procedure, a technique of direct access to non-weight-bearing areas with tumoral bone involvement was developed.[2,3,10,16] For these treatments, the use of NBCA was advocated, and produced a good occlusive effect on the parenchyma of highly vascular tumors. Histology revealed extensive intralesional necrosis.[16] The antitumoral effect of the NBCA at the implant surface on adjacent tumor appeared limited.[16]

The purpose of this paper is to illustrate and further discuss the extended effect of PMMA, when compared with NBCA.

Materials and Methods

Direct intratumoral injection of acrylic implants has been used at our institution in the last 4 years for 40 vertebroplasty (PMMA) procedures and for nine bone lesions of other locations (PMMA, NBCA). Histology became available for 1 case of PMMA and

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8756-3282/99/$20.00
PII S8756-3282(99)00140-4

Bone Vol. 25, No. 2, Supplement
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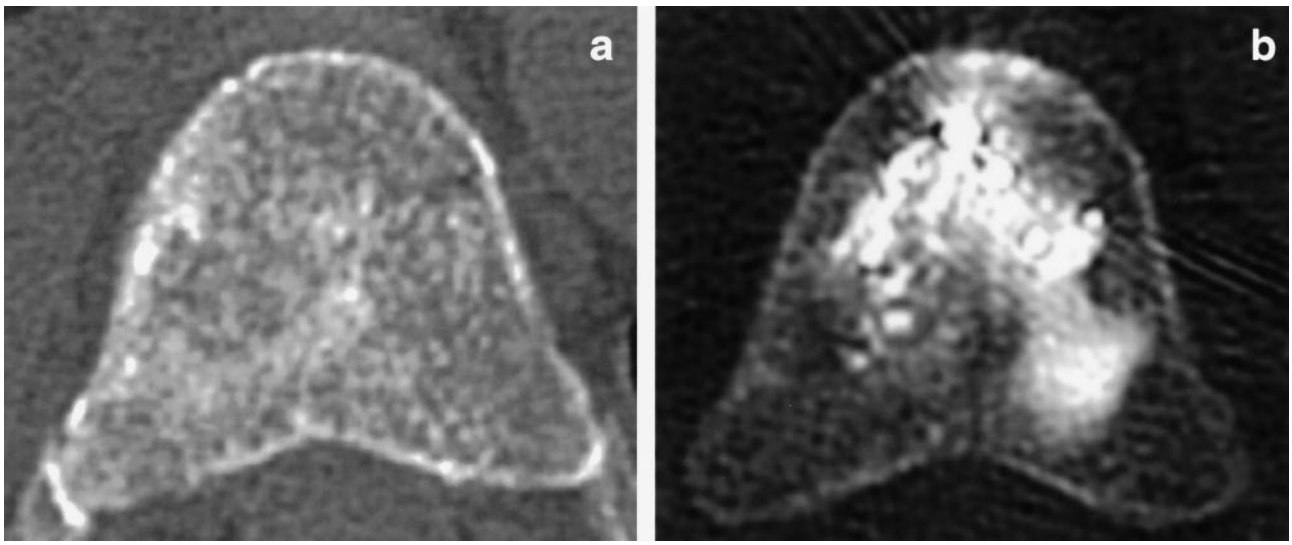

Figure 1. (a) Pretreatment CT of D6 vertebral body. (b) Posttreatment CT of D6 vertebral body. Note extension of radiopaque PMMA implant.

for 5 cases with NBCA intratumoral acrylic implants. One case of each type of implant is used to illustrate these findings.

We present the histopathology findings of two cases of different tumors treated by acrylic cement in an attempt to better understand the mechanisms of acrylic action in vivo. The first findings relate to a case of painful vertebral metastasis of an adenocarcinoma of probable bronchial origin, treated by transpedicular percutaneous vertebroplasty. We compare this case with a case of a malignant, highly vascularized para-ganglioma of the pelvis that was treated by a two-step procedure using direct puncture embolization of the tumor with NBCA, followed by surgical resection.

Case 1

A 68-year-old woman with generalized adenocarcinoma of probable pulmonary origin presented with severe back pain at a mid-thoracic level. Magnetic resonance imaging (MRI) revealed bone metastasis of the vertebral bodies at D6 and D8 levels, with diffuse involvement of both vertebral bodies and a partial collapse of the D8 vertebral body. No extension into the perivertebral compartments and no destruction of the posterior vertebral wall were noted. After a pretreatment computed tomography (CT) (**Figure 1**a), vertebroplasty was performed at both levels after unilateral left-sided percutaneous, and transpedicular approach was gained at each level using fluoroscopy control.[6,7] A diluted PMMA mixture (20 mL powder for 5 mL liquid, and 1 g of Tungsten powder as contrast-enhancing additive) was injected as implant using a total volume of 4 mL PMMA mixture (Simplex P, Methyl-methacrylate; Howmedica Inc., Rutherford, NJ). Posttreatment CT demonstrated the implant distribution within the vertebral body (Figure 1b). The procedure allowed for lasting pain relief. Six months after the procedure, the patient died of extensive metastatic spread, as confirmed by autopsy. The nondecalcified vertebral body of D6 was embedded in PMMA resin and cut using a tungsten carbide knife microtome to provide histological transverse sections of the entire vertebral body (**Figure 2**). Special attention was given to the tissue reaction and tumor residues in the environment of the PMMA implant.

Case 2

A 54-year-old man was investigated for progressive severe pain of the left inguinal region. Conventional radiography, pelvic CT, and MRI revealed a highly vascular lesion of $8.8 \times 8.5 \times 7$ cm size. Surgical biopsy confirmed this lesion to be a malignant para-ganglioma, infiltrating the left superior ramus of the pubis, and identified it as the original metastatic site of a previously treated lesion of the right distal femoral diaphysis. Presurgical preparation required devascularization of the lesion and occlusion of the internal iliac branches. Digital subtraction angiography (DSA) revealed a rich vascular supply and an important tumor blush (**Figure 3**a). Direct percutaneous access was gained using 20-G needles. Visualization of the tumor parenchyma was achieved by injecting contrast material through the needle (Figure 3b). This allowed for estimation of the tumor compartment potentially addressed by the subsequent acrylic injection. NBCA (Histoacryl; Braun, Melsungen, Germany) was mixed with ethiodol (Lipiodol ultra-fluide; Laboratoire Guerbet, Aulnay-sous-Bois, France) at equal amounts[2,3] and injected in a stepwise fashion for a total of 86 cc polymer mixture. Subsequent contrast material injections into the internal iliac artery on the left were used to guide the procedure, involving further stepwise and multiple direct punctures and polymer implantation procedures. After almost total acrylic filling of the tumor, the arterial branches of the left internal iliac artery close to the tumor were occluded with endovascular injection of silk suture segments (size 4.0 for a total length of 6 m). A good devascularization was obtained, facilitating surgery 3 days later. Histological slides of the tumor were prepared and special attention was given to the tissue reaction and tumor residues in the environment of the NBCA (**Figure 4**). A small focus of residual tumor (containing mostly NBCA) visualized by CT (Figure 3c) was treated with complementary radiotherapy. Twelve months later, CT (Figure 3d) and MRI showed local tumor recurrence adjacent to the remaining acrylic implant.

Histology Findings

Case 1. Microscopical findings of D6 vertebral body were studied (toluidine blue and hematoxylin & eosin [H&E] stains). The central part of the body contained several large empty spaces,

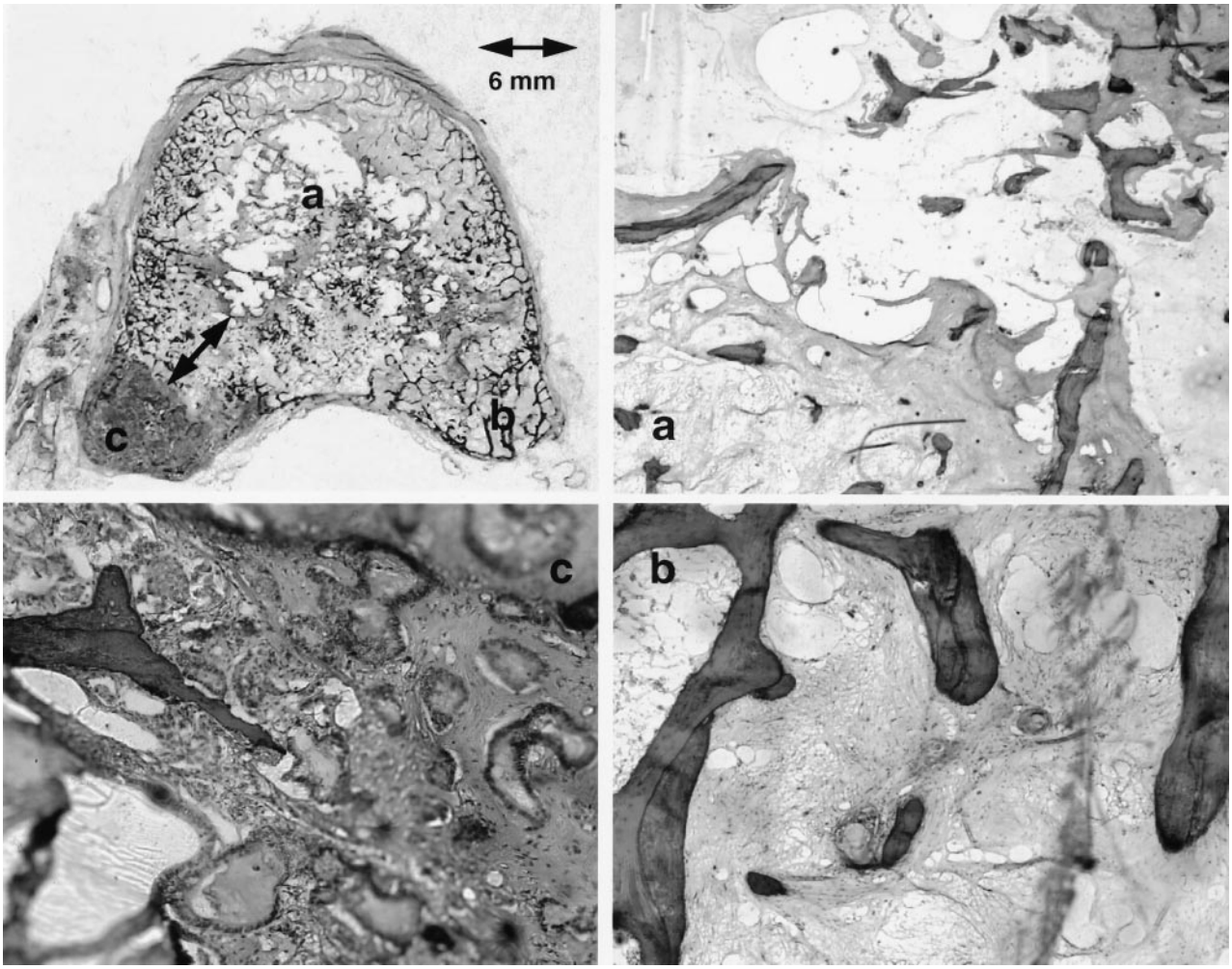

Figure 2. Transverse section through D6 vertebral body, view from below, according to CT (Toluidine blue, no magnification). This section shows PMMA implant (void with irregular contours) within the central aspects of the vertebral body and in the region toward the left vertebral pedicle. There is a zone of tumor residual in right pedicle (left). Note the 6-mm distance (double-headed arrow) corresponding to the rim of tumor necrosis around the PMMA implant. (a) Note central portion of vertebral body with PMMA (void), surrounded by reactive fibrosis and bone trabeculae (H&E, original magnification ×50). (b) Left pedicle showing three residual tumoral foci (H&E, original magnification ×50). (c) Right pedicle with residual tumor infiltration (H&E, original magnification ×100).

which corresponded to the PMMA implant washed out by the staining procedure. Residual bone in this area showed signs of active remodeling. In between the implant, pale outlines of necrotic tumor glands and calcification were seen focally within the fibrotic medullary spaces. This was interpreted to represent necrotic tumor captured within the implant (Figure 2a).

Towards the periphery, foreign body giant cells occasionally bordered smaller areas of the PMMA implant. Here, as in the left pedicle (injection site), isolated tumor glands were seen (Figure 2b). The almost complete necrosis observed in the vicinity of the PMMA implant formed a rim averaging 5 mm (range 3–11 mm) in diameter around the PMMA (Figure 2). The nontreated right pedicle contained diffusely infiltrating tumor (Figure 2c). Tumor infiltration was also found in the perivertebral connective tissue, with presence of lymphatic and perineural spread.

Case 2. Microscopic findings of the surgically resected piece were studied (H&E stain). Viable tumor tissue, situated peripherally, consisted of nests of large cells with clear cytoplasm and large nucleolated nuclei, surrounded by a fine capillary network. Some areas of tissue deformation were seen due to mass effect produced by the implant.

Towards the tumor surface, NBCA-related cavities were found without surrounding tumor necrosis (Figure 4a,b). In regions towards the tumor center, the sample contained large voids corresponding to washed out acrylic fillings. These areas also contained regions of necrotic tumor tissue (Figure 4c,d). A mild inflammatory response consisting of polymorphonuclear neutrophilic infiltrates was seen around some necrotic areas. There were no foreign body giant cells, and fibrosis was absent.

Discussion

The PMMA vertebroplasty case provides evidence of important tumoral destruction by the PMMA implant. Postmortem, histological preparation of the injected vertebral body, 6 months after procedure, shows close to complete tumoral necrosis in the region of the PMMA implant. More importantly, the tumoral necrosis extends beyond the immediate vicinity of the implant, to

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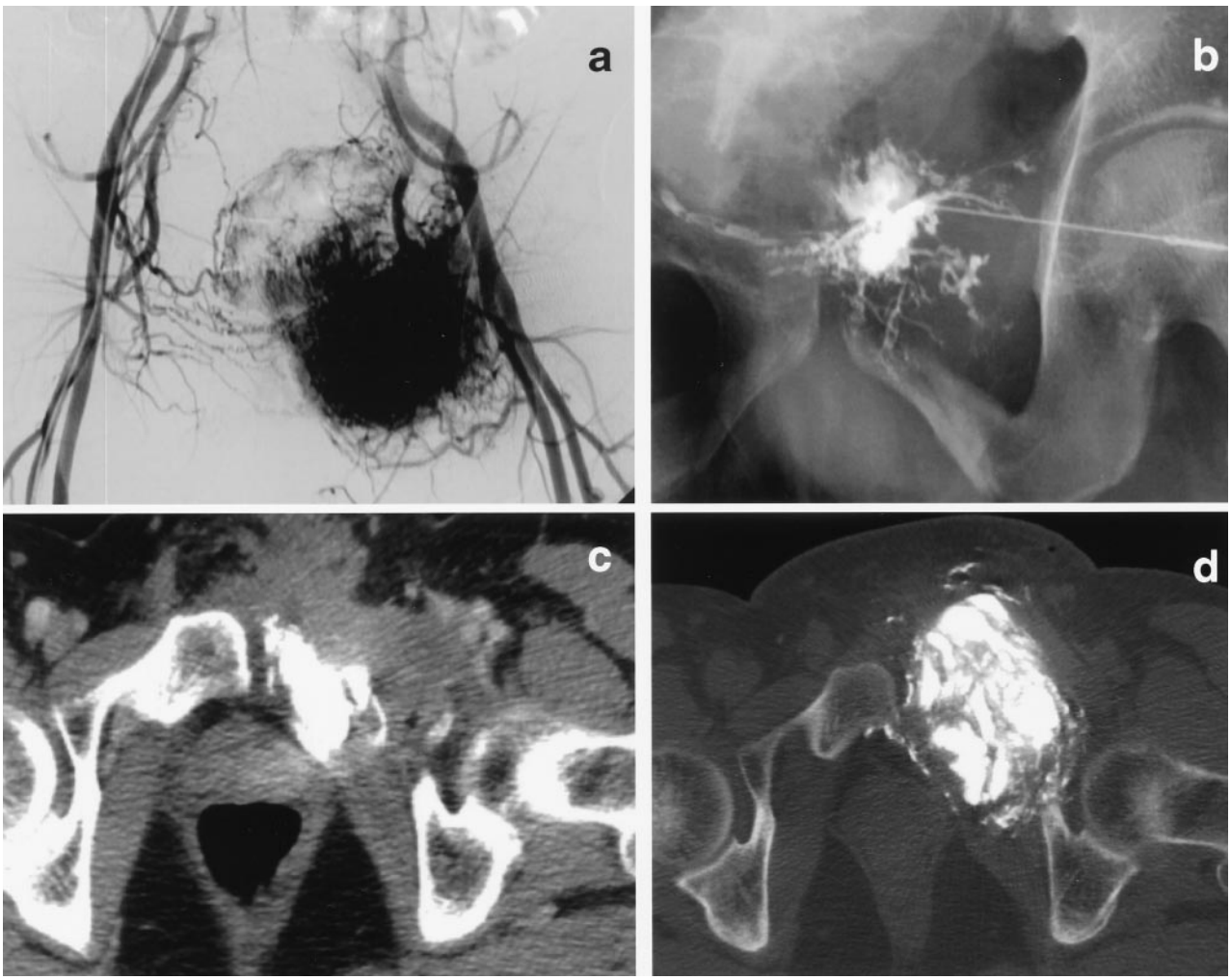

Figure 3. (a) Global angiography of pelvic region revealing the highly vascular tumor with extensive arterial tumor blush. (b) Direct access to the tumor parenchyma and associated draining veins by percutaneous puncture with a 20-G needle allowing for contrast material injection and subsequent plastification of the tumor accordingly. (c) Posttreatment CT after incomplete surgical removal with residual tumor area opacified by NBCA implant. (d) Follow-up CT 1 year later shows local recurrence adjacent to the plastified tumor area.

a distance of 11 mm. Within regions of tumoral necrosis, occasional sparse clusters of two to three tumoral cells remain. The antitumoral effect in this case can probably be attributed to the above-mentioned causes, i.e., thermal necrosis and direct toxicity of the implant. Arterial and venous ischemic necrosis is probably also largely implicated, as there is an important mass effect exerted by the implant.

In this case, compact tumoral tissue remains in the right pedicle, where no PMMA implant could be found. All of the cement was injected through the left vertebral pedicle and failed to fill the vertebral body region juxtaposing the right vertebral pedicle and the right vertebral pedicle itself. This raises the question of the indication for extensive PMMA fillings with a bilateral transpedicular injection of the vertebral body. Although a unilateral approach might be sufficient for satisfactory filling of the vertebra in terms of stabilization of the vertebra and subsequent pain relief, it might not be sufficient when an additional antitumoral effect is desired.

The original tumor in this case was a well-differentiated adenocarcinoma of probable bronchial origin. It remains to be seen if the antitumoral effect observed here is reproducible and whether it applies to other tumors as well. It is likely that different tumors will exhibit different sensitivities to the antitumoral effect of the PMMA implant used.

The second findings are those of a case of malignant pelvic para-ganglioma that was surgically removed after a percutaneous injection of NBCA. Histopathological examination revealed regions of NBCA presence and variable degrees of tumoral necrosis around it. Areas surrounding small volumes of NBCA at the periphery of the tumor show practically no necrosis, while regions inside the tumor plastified with NBCA present greater degrees of necrosis, especially toward the center of the tumoral mass. It is noteworthy that polymerization of NBCA is less exothermic than PMMA.[18] Since the tumor was resected only 3 days after the NBCA injection, the time lapse is too short to evaluate the presence of a toxic effect from the NBCA. Therefore, we conclude that tumoral necrosis in this case is most likely of an ischemic nature related to plastification of the vascular tumor parenchyma and to mass effect. No necrosis was found in areas close to the surface where a continuous vascular supply exists, coming from the peritumoral environment.

Since the surgical resection was incomplete towards the symphysis, a plastified tumor compartment remained. A follow-up CT and DSA at 12 months showed a local recurrence of

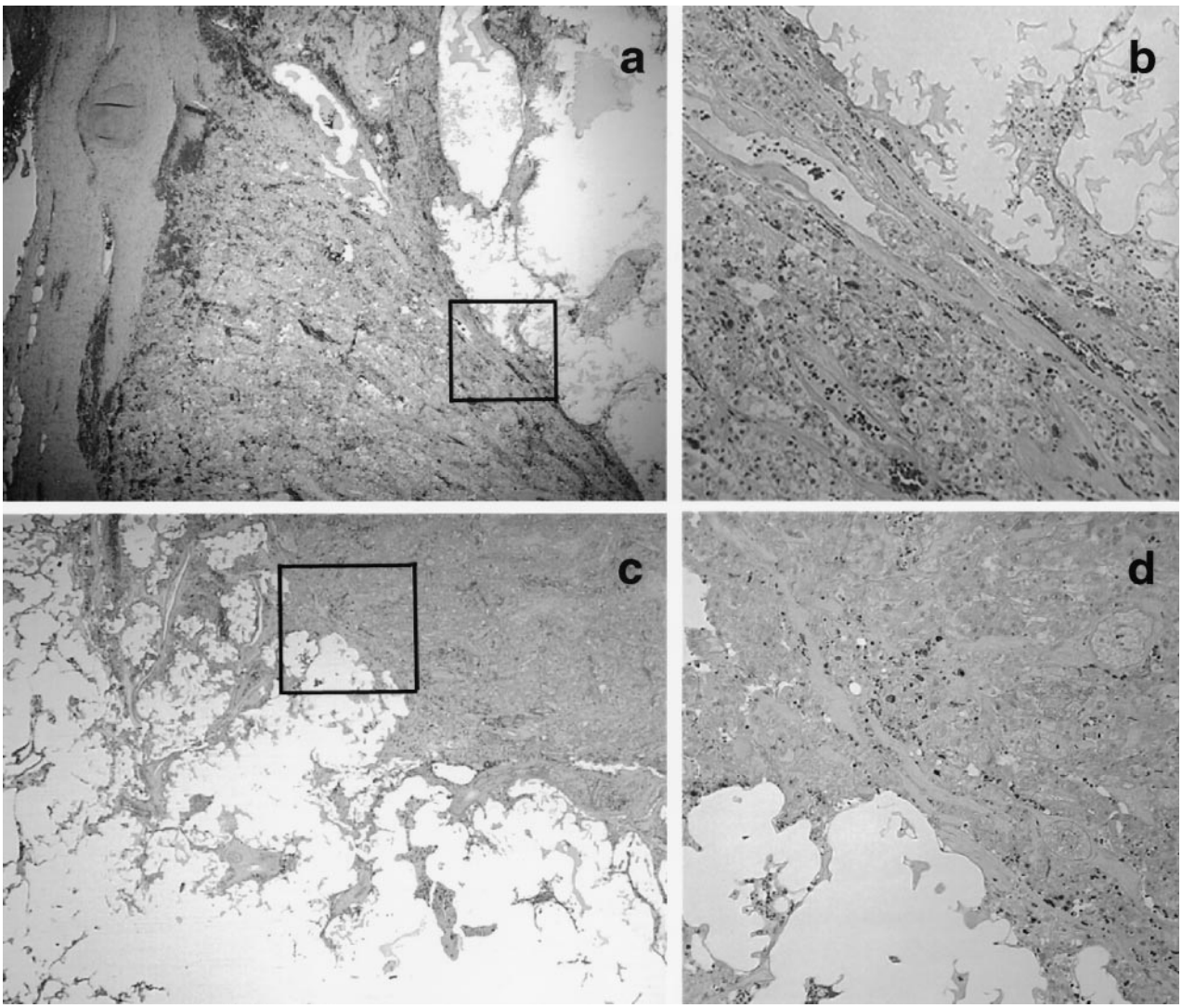

Figure 4. Histological section of resected paraganglioma after percutaneous NBCA injection. (a) Section close to the tumor surface showing NBCA (void) and viable tumor around the implant (H&E, original magnification ×25). (b) High-power view of a. Note absence of necrosis around the implant (H&E, original magnification ×100). (c) Section in a deeper zone of the tumor. Note extensive necrosis (H&E, original magnification ×25). (d) High-power view of c. Note an acellular necrotic area (H&E, original magnification ×100).

the tumor in the periphery of the cement, while the cast of NBCA remained basically unchanged in its appearance. This local recurrence probably originated from a superficial tumoral region not plastified by NBCA fillings.

These two cases illustrate two different degrees of tumoral necrosis obtained by injection of acrylic implants. Both PMMA and NBCA allowed for destruction of tumor tissue within heavily plastified areas. With PMMA, the necrosis overextends the immediate vicinity of the implant, while with NBCA, no necrosis was found at a macroscopic level outside the implant.

More studies are necessary to provide further information on the antitumoral effects of acrylic implants and the different tumoral responses according to tumoral type. This may be particularly important in cases where tumors cannot be completely filled with acrylics or resected, thus leaving viable tumoral tissue in situ, at high risk of recurrence. It also raises the question of an indication for a greater use of acrylic implant mixtures containing radioactive isotopes or cytotoxic agents such as methotrexate.[19] Future implant development should consider the interest of implants extending their antitumoral activity at a distance of 5–10 mm beyond the limits of the implant.

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