

# Frequency of translocation of USP-6 in the aneurysmal bone cyst of the jaw

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## Abstract

**Background:** This study aims to detect USP6 translocation in aneurysmal cysts located in the jaw and to give an overview of demographic data.

**Methods:** The present retrospective cohort study includes 10 patients who underwent surgery due to an aneurysmal cyst of the jaw in our hospital between 2002 and 2021. Unstained formalin-fixed and paraffin-embedded tissue sections cut at 4 µm thickness were subjected to USP6 FISH testing.

**Results:** All patients underwent surgical treatment. In four of ten patients (40%) USP-6-translocations have been found.

**Conclusion:** Based on the study, it is hypothesized that the aneurysmal bone cyst of the jaw bone may be subject to a different pathomechanism than that of the long bones. Therefore, it seems conceivable that the primary cause of aneurysmal bone cysts in the jaw might differ.

## KEYWORDS

aneurysmal bone cyst, jaw, USP-6 translocation

## 1 | INTRODUCTION

The aneurysmal cyst of the bone is a rare bone lesion and is mainly found in the metaphysis of long bones and the spine.<sup>1,2</sup> The aneurysmal cyst of the bone was first described by Jaffe et al. (1942)<sup>3</sup> and counts as its own entity. Histopathologically it represents itself as a multicystic lesion with fast and aggressive growing patterns.<sup>4</sup> Recurrence rates have been reported between 10% and 59% after surgical treatment. Reasons and risk factors for developing aneurysmal cysts of the bone are discussed controversially. Malformations of vessels or hemodynamic perturbances are discussed in the literature.<sup>5</sup> Aneurysmal bone cysts of the jaw are considered to be very rare and account only for 1.9% of all bone lesions in the head and neck area.<sup>6,7</sup> Assumptions regarding the etiology, the risk factors discussed, and the recurrence rates mainly refer to known results from the long tubular bones. The data concerning the aneurysmal bone cysts of the jaw is indistinct.

Panoutsakopoulos et al.<sup>8</sup> and Oliveira et al.<sup>9</sup> finally discovered that a chromosomal aberration (16;17) (q22;p13) results in a fusion of the USP-6 gene and subsequent overexpression of this gene. USP-6 is a ubiquitin-specific protease, first discovered in 1992 in Ewing-Sarcoma as a potential oncogene.<sup>10</sup> Fusion of the promoter and USP-6 leads to angiogenesis and osteoblastic differentiation.<sup>11</sup> This translocation was detected in 69% of aneurysmal bone cysts by fluorescence in situ hybridization (FISH).<sup>9</sup> In healthy adult patients, USP-6 is hardly expressed in other localization except the testis and ovary and is basically specific for tumor cells. Studies by Oliveria et al have shown that it is absent from inflammatory cells, endothelial cells, osteoblasts, and other multinuclear giant cells.<sup>12</sup>

Several studies performed FISH, but without distinguishing different anatomical localization of aneurysmal bone cyst. The data in the literature mainly refers to aneurysmal cysts in the long tubular bones; whether USP-6 is implicated at all and in which rate in the jaw is

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unclear. Other authors suspected that some of the cysts in the jaw region were more reactive in nature and thus different from the more typical neoplastic ones in the long tubular bones.<sup>13</sup>

In clinical practice, the correct diagnosis is always a challenge and can often only be made in combination with clinic, radiology, and histopathology. At this point, markers such as USP-6 can facilitate this diagnosis and, if necessary, confirm it. It is unclear to what extent the marker USP-6, which is established in the long tubular bone, is suitable for the jaw. At this point, markers such as USP-6 can facilitate this diagnosis and, if necessary, confirm it.

This study aims to detect USP6 translocation in aneurysmal cysts located in the jaw and to give an overview of clinical data.

## 2 | MATERIALS AND METHODS

The institutional review board approved this study of the University Hospital of Munich, Germany (Munich, Germany, 22-0091). The present retrospective cohort study includes 10 patients who underwent surgery due to an aneurysmal cyst of the jaw in our hospital between 2002 and 2021. Only patients with available histopathological reports and available specimens were included in this study.

Patient records and all available documents, as well as radiographs, were reviewed retrospectively. FISH was performed in cooperation with the Pathology Institute LMU Munich.

Unstained formalin-fixed and paraffin-embedded tissue sections cut at 4  $\mu$ m thickness were subjected to USP6 FISH testing.

Slides were deparaffinized in xylene and rehydrated in ethanol descending before pretreatment with Digestion Enzyme (Life Technologies, Grand Island, NY) for 30 min at 37°C, dehydration in ethanol from 70% to 100%, and codenaturation at 85°C with the ZytoLight SPEC USP6 (17p13) Dual Colour Break Apart Probe (-Zytovision, Bremerhaven, Germany) for 20 min. After hybridization, slides were washed in 0.4X saline for 2 min at 74°C and mounted with Vectashield containing 4',6-diamidino-2-phenylindole (DAPI) at a concentration of 1.5  $\mu$ g/ml (Vector Laboratories, Burlingame, CA).

Two independent, experienced pathologists scored USP6 signals. The cut-off for positive is at least 10% of the 100 counted tumor cells showing split signals. In the cases of secondary ABC, both the primary tumor and secondary ABC areas were evaluated for USP6 rearrangement.

### 2.1 | Statistical analysis

Statistical analysis was conducted using SPSS® 24 version 4.0 (SPSS Inc., Chicago, IL). Due to the low number of patients, only descriptive statistics were performed using figures and tables. Normally distributed data were presented using mean  $\pm$  standard deviation (SD), and Non-normal distributed data was illustrated by depicting median and interquartile ranges.

## 3 | RESULTS

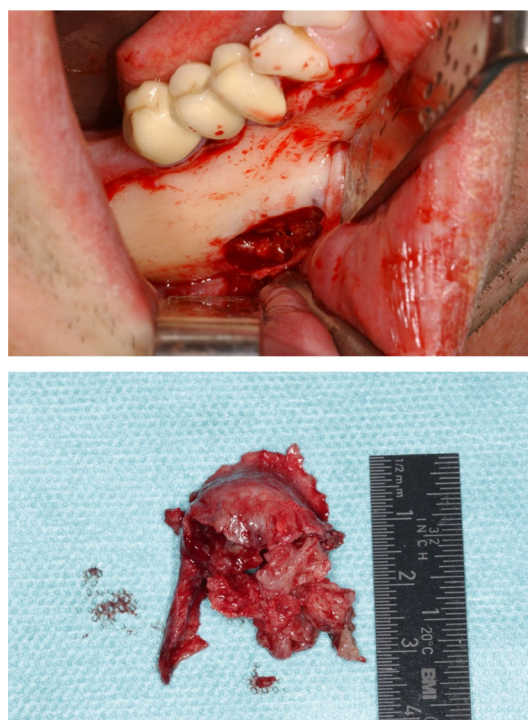
Overall, 10 patients could be included in this study. Four of them were male (40%), and six (60%) were female. All patients were Caucasian type. The average age at primary diagnosis amounted 22.9 years  $\pm$ 10.48 years:

In six patients localization was in the jaw angle, in one patient on the temporo-mandibular joint, in one patient in regio 33 and in two patients on the ramus.

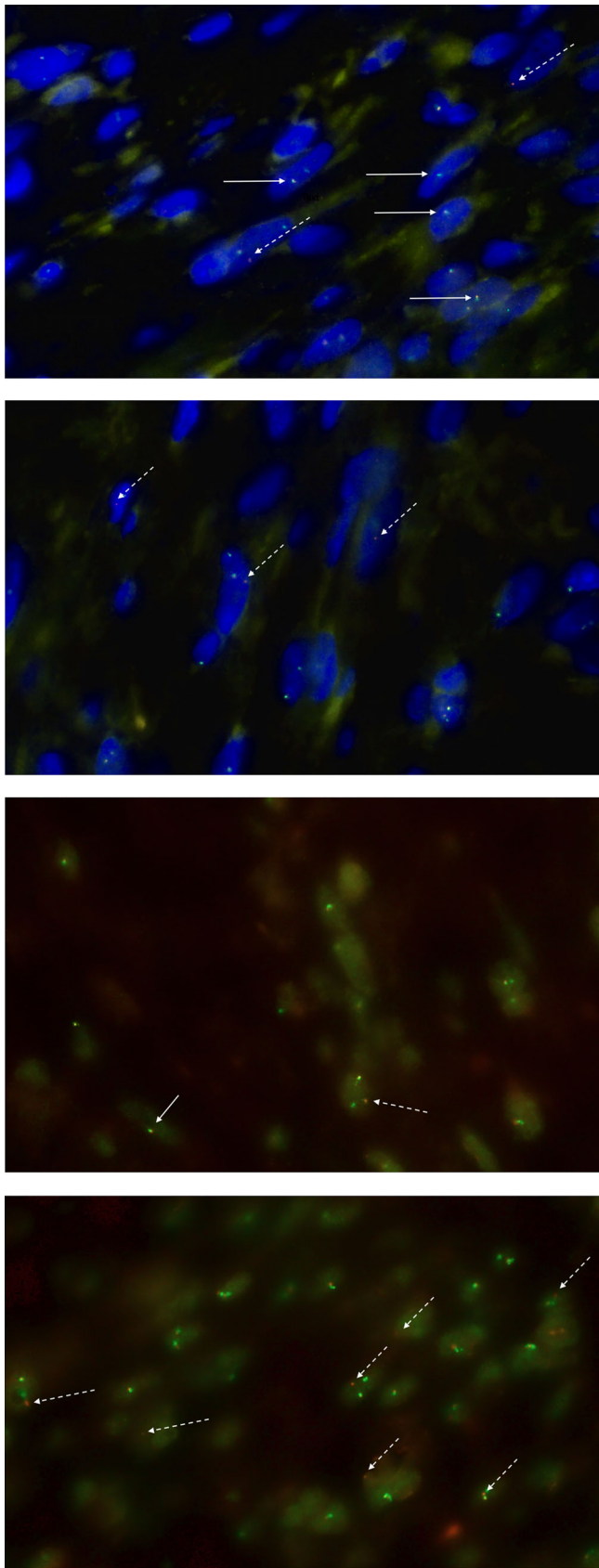
The average diameter of an aneurysmal bone cyst was 1.67 cm  $\pm$  1.13 cm, average tumor thickness was reported to be 0.49 cm  $\pm$  0.36 cm. Panoramic x-ray (Figure 1) was available in every patient, computed tomography (CT) (Figure 1) in three cases, MRI in two



**FIGURE 1** Radiographic data. Panoramic x-ray of aneurysmal bone cyst



**FIGURE 2** Intraoperative photographs of aneurysmal bone cyst



**FIGURE 3** Colocalization of the fluorescence signals indicates translocation of USP-6

cases, and digital volume tomography (DVT) in four cases. None of the patients suffered from a jaw trauma as a possible reason for the aneurysmal bone cyst. Local recurrence was found in one patient.

All patients underwent surgical treatment was performed in all cases. Figure 2 shows intraoperative taken photos of the aneurysmal bone cyst.

In four of ten patients (40%) USP-6-translocations have been found. Microscopically, the aneurysmal bone cyst was mainly composed of blood-filled cystic spaces separated by fibrous septa. The fibrous septa were composed of a moderately dense cellular proliferation from bland fibroblasts with scattered, multinucleated, osteoclast-type giant cells. Figure 3 shows the results of USP-6 translocation.

#### 4 | DISCUSSION

The aneurysmal cyst of the bone accounts for the nonneoplastic lesions of the bone and is a relatively uncommon finding in the facial bones. Between 1.8% and 1.9% of aneurysmal cysts are located in the jaw.<sup>6,7</sup> Our department, a university hospital, could report about 10 cases within more than two decades. The typical time of arising is during the second decade of life, according to our data, where the mean age amounted to 22.9 years. Prevalence is slightly higher in female patients, as shown in our data (60% female). The most common localization in our data was the jaw angle (80%). Only in one case, the aneurysmal bone cyst was located in the temporomandibular joint, and in another case, in the mandible regio 33. This is similar to other studies. A systematic review reports the mandible jaw to be the most common localization (24.4%).<sup>14</sup> All 10 patients underwent surgical treatment with cystectomy and curettage. In parts of Europe, aneurysmal bone cysts are sometimes treated like a malignant tumor with standard contour resection and safety margin due to the high recurrence rate of up to 40% described in the literature.

Álvarez-Martínez et al. 2019<sup>15</sup> report about a case with a large aneurysmal bone cyst treated with surgical therapy meaning osteotomy and curettage. The treatment options are percutaneous sclerotherapy, diagnostic and therapeutic embolization, curettage, block resection and reconstruction, radiotherapy, and systemic calcitonin therapy.<sup>14</sup> Simply curettage is reported to come with a higher rate of local recurrence after surgery.<sup>16</sup> Rare self-healing cases are described as well in literature, but due to the growth pattern of aneurysmal bone cyst is not recommended as standard therapy.<sup>17</sup>

Local recurrence appeared only in one patient, aneurysmal bone cyst of the bone was located at the temporomandibular joint and expanding to the cranial base. Surgical treatment was performed by cystectomy combined with craniotomy. Compared to the literature, the relatively low recurrence rate here may be due to the different specialties and the associated different therapeutic concepts. Our standard cystectomy with a minimal safety margin in milling out the lumen showed good results.



USP-6 translocation was first reported by Panoutsakopoulos et al. 1999.<sup>8</sup> Recurrent chromosome aberration t(16;17) (q22;p13) leads to a fusion gene of the entire ubiquitin-specific protease 6 (USP6 alias Tre2) coding sequence at 17p13. an upregulated expression of the otherwise structurally and functionally intact USP6 leads to angiogenesis and has an influence and cell signaling.<sup>17</sup> Considering all possible localizations of the aneurysmal bone cyst, USP6 translocation can be found between 69% to even a 100% depending on the study.<sup>18,19</sup> In the above mentioned studies all localizations of aneurysmal bone cysts were included, but most of the cases were located in the long bones.

In our study, only aneurysmal bone cysts of the jaw were considered only 40% showed USP6-translocation. This leads to the assumption that perhaps other molecular mechanisms independent of USP-6 could play a role in the aneurysmal bone cyst of the jaw. Key for the development of aneurysmal bone cysts seems to be the Jak1-STAT3.

Studies have shown that Jak1 is the first direct substrate of USP-6, and thus Stat3 is activated indirectly by USP-6.<sup>20</sup> This signaling pathway is essential for tumorigenesis. Furthermore, the production of autocrine/paracrine factors by USP-6 expressing cells leads to a sensitization for the Jak1-STAT3 pathway. This results in a positive feedback loop. Jak1-STAT3 signals are essential effectors of the USP6.<sup>20</sup>

The question arises whether the cyst of the jaw finally corresponds to the entity of the cyst of the long tubular bones or whether it changes around another pathology that is only very similar to that of the long tubular bones.<sup>13</sup> Regarding the expression pattern, there seem to be variations. It may be necessary to differentiate between an entity of aneurysmal bone cysts expressing USP-6 induced by this translocation and USP-6 negative ones, which may have a different etiology or the above mentioned pathway is influenced in an other way which remains unknown at the moment.

Pathologic evaluation of the solid variant of aneurysmal bone cysts with USP6 rearrangement with an emphasis on the frequent diagnostic pitfalls.<sup>13,20,21</sup>

Further studies in aneurysmal bone cysts should examine different molecular pathways and proteins. Why USP-6 translocation is lower in the jaw than in the long tubular bone remains unclear. There may be other underlying pathologies that lead to the same clinical picture as the USP-6 translocation or it may be a different entity. This could help in clinical management and could lead to possible new medical therapies.

## 5 | CONCLUSION

The study was able to show that in our patient population, the USP-6 translocation is detectable in only one-third of the cases. This is lower compared to the literature and compared to aneurysmal bone cysts of the long bones.

### AUTHOR CONTRIBUTIONS

Katharina Theresa Obermeier and Selagi Haidari were responsible for conceptualization, methodology, data curation writing and validation;

Sven Otto was responsible for data curation and review; Elisa Schmöckel performed FISH-analysis and was responsible for review and editing and formal analysis; Katharina Theresa Obermeier and Selagi Haidari were responsible for review and editing and methodology; Sven Otto was responsible for review and editing; Sven Otto was responsible for review and editing and supervision; Katharina Theresa Obermeier and Selagi Haidari were responsible for conceptualization, methodology, data curation writing and validation.

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### CONFLICTS OF INTEREST

The authors have no conflicts of interest.

### PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/jop.13393>.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not open available due to ethics statement.

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