Review Article

Giant Cell Tumor of Bone: A Neoplasm or a Reactive Condition?

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Abstract: Giant cell tumor of bone (GCTB) is a benign but locally aggressive bone tumor of young adults. It typically presents as a large lytic mass at the end of the epiphysis of long bones. Grossly it is comprised of cystic and hemorrhagic areas with little or no periosteal reaction. Microscopically areas of frank hemorrhage, numerous multinucleated giant cells and spindly stromal cells are present. Telomeric fusions, increased telomerase activity and karyotypic aberrations have been advanced as a proof of its neoplastic nature. However such findings are not universal and can be seen in rapidly proliferating normal cells as well as in several osseous lesions of developmental and/or reactive nature, and the true neoplastic nature of GCTB remains controversial. The ancillary studies have generally not reached to the point where these alone can be taken as sole diagnostic and discriminatory criteria. While giant cells and stromal cells have been extensively studied, little attention has been paid to the overwhelming hemorrhagic component. If examined carefully intact and partially degenerated red blood cells are almost invariably seen in many giant cells as well as in the stroma. While hemorrhage in many patients may be resolved without leaving any trace over time, in some it gives rise to giant cell formation, and in others it may lead to proliferation of fibroblasts and histiocytes. At times one sees xanthomatous cells due to intracytoplasmic cholesterol deposits and sharp cholesterol clefts. Individual genetic makeup, local tissue factors as well as the amount of hemorrhage may play a key role in the final effects and outcome. Malignancy usually does not occur in GCTB and when discover, it usually represents primary bone sarcomas missed at original diagnosis. Embolization therapy to curtail hemorrhage and insertion of cement substance to support matrix are helpful in reducing recurrences. Aneurysmal bone cyst (ABC) shares many features with GCTB. There had been unique karyotypic changes in some aneurysmal bone cysts making it distinct from GCTB. However these changes may be in the endothelial cells which are quite different from stromal or giant cells. It had been concluded that the poor matrix support to the vessels may lead to frequent and profuse intraosseous hemorrhage attracting blood-derived monocytes with active conversion into osteoclasts, resulting in GCTB formation. On the other hand, dilatation of the thin-walled blood vessels results in formation of ABCs. If hemorrhagic foci are replaced by proliferation of fibroblasts and histiocytes, then a picture of fibrous histiocytic lesion is emerged. Enhanced telomerase activity and karyotypic aberrations may be necessary for rapid division of the nuclei of the giant cells in order to be able to deal with significant in situ intraosseous hemorrhage.

Key Words: Giant cell tumor, bone, osteoclastoma, aneurysmal bone cyst, osteoclast, hemorrhage, bone matrix, telomerase

Introduction

The giant cell tumor of bone (GCTB) is a benign but locally aggressive bone tumor of young adults of 20-40 years of age. It constitutes about 4-5% of all bone tumors and about 18% of all benign bone tumors. It is slightly more common in females. Chinese have a slightly higher incidence of GCTB, up to 20% of all benign tumors of bone. The tumor presents as a large lytic mass of the epiphysis of long bones, particularly lower femur, upper tibia and lower radius (Figure 1).

GCTB is generally considered a true neoplastic condition with well-defined clinical, radiological and histopathological features [1, 2]. Radiologically, it is usually lytic and expansile without prominent peripheral sclerosis and periosteal reaction [3]. Some pathologists consider it a low grade or potentially malignant neoplasm [4-6]. The tumor is locally aggressive and destructive, and it tends to recur after simple curetting. In addition to its
Figure 1 A lytic expansile lesion with multiple septae involving the first metacarpal bone. The tumor was histologically proven GCTB.

frequent association with aneurysmal bone cyst (Figure 2) and slightly higher incidence in Paget’s disease of bone, many lesions closely mimic GCTB. These include brown tumor in hyperparathyroidism, expansile metastasis from renal cell carcinoma and thyroid carcinoma, hemophilic pseudotumor with hemorrhage, Infestation of bone by a hydatid cyst and telangiectatic osteosarcoma.

The histopathology of GCTB is characterized by frank and marked hemorrhage, numerous giant cells and stromal cells [2, 7]. The hemorrhage gives rise to the characteristic grossly lytic picture. Many workers have totally ignored this component and did not emphasize the role of multinucleated giant cells in the removal of hemorrhage although such is observed in different pathological lesions such as adenomatous goiter, brown tumor of hyperparathyroidism and giant cells in reparative granulomas. The giant cells are considered reactive while stromal cells are considered “true” neoplastic cells with little or any justification. There had been a lot of debate about the origin of both types of cells. There is now agreement that giant cells are circulating monocytes in origin which have converted into osteoclasts after acquiring some unique features and gene expressions in osseous environment. These conclusions are based on various light, ultrastructural and immunological markers [8-12]. On the other hand, the stromal cells are generally regarded as fibroblasts secreting type I and III collagen and having parathormone receptors [13-18].

Giant cells have the characteristic features of several mycobacterial, fungal and parasitic diseases as well as sarcoidosis and foreign bodies. Several non-infectious and non-granulomatous pathological lesions other than GCTB also contain large number of giant cells; most if not all of these are considered reactive rather than neoplastic.

In this article we will briefly review various concepts and proposals about the origin of GCTB, giant cells and stromal cells in GCTB. Based on these as well as on our own experience and observations, we consider GCTB a non-neoplastic albeit aggressive reactive "tumor" which most likely originates on the basis of hemorrhage resulting from weak local vasculature, which in turn could be due to local defect in the supporting matrix. In this regard aneurysmal bone cyst (ABC) and some fibrous histiocytic growths share the same etiopathogenesis with dominance of different morphological components, i.e., giant cells in GTCB, markedly dilated vessels in ABC and prominent fibroblasts and histiocytes in
### Table 1 Etiological, gross and microscopic comparison of various giant cell-rich lesions

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Cause</th>
<th>Gross features</th>
<th>Microscopic features</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCTB</td>
<td>Matrix and / vessel collagen defect leading to poor support to the vessels and hemorrhage</td>
<td>Large lytic and destructive lesion in the epiphysis</td>
<td>Predominantly multinucleated giant cells each containing red cells and their components. Foci of hemorrhage and activated stromal cells</td>
<td>Not a true neoplastic tumor. Reactive tumor due to hemorrhage, large number of giant cells and reactive stromal cells</td>
</tr>
<tr>
<td>ABC</td>
<td>Matrix and / vessel collagen defect leading to poor support to the vessels and predominantly markedly dilated vessels and some hemorrhage</td>
<td>Markedly ballooned vessels giving rise to a &quot;cyst&quot; appearance</td>
<td>Large thin-walled, markedly dilated vessels and evidence of hemorrhage and few giant cells.</td>
<td>Not a true neoplastic tumor. Reactive condition due to thin-walled dilated vessels which in turn are mostly due to poor support of the matrix suggesting a primary matrix defect in epiphyseal area</td>
</tr>
<tr>
<td>Fibro-histiocytic lesion</td>
<td>Predominantly stromal cell response to foci of hemorrhage</td>
<td>Local osseous density</td>
<td>Proliferation of active fibroblasts and histiocytes.</td>
<td>Not a true neoplastic tumor. Reactive condition due to excessive fibro-histiocytic stimulation and proliferation</td>
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fibrous histiocytic lesions.

Hormonally-induced hyper-dynamic metabolic events may also lead to hemorrhages giving rise to lesions similar to GCTB notwithstanding in more widespread and diffuse patterns. Excessive parathyromone thus causes ostelitis fibrosa cystica and brown tumor very closely resembling GCTB microscopically. Likewise reparative granuloma of head and neck region may have similar pathogenesis. Thyroid gland under iodine deficiency stress and rebound stimulation undergoes hypervascularity which on palpation gives rise to hemorrhage and hemosiderin-containing giant cells in adenomatous goiter. If the process is not reversed in time, exuded red cells and plasma leads to fibrosis converting diffuse goiter into multi-nodular goiter.

### Origin of Giant Cells and Stromal Cells

Except for true neoplastic and dysplastically malformed giant cells, almost all other giant cells are of macrophage lineage (Table 1). With repetitive nuclear divisions unaccompanied by cytoplasmic division, multinucleated giant cells are formed. This process may require heightened telomerase activity and some gene rearrangement. Exposure to certain infectious agents and endogenous or exogenous foreign substances bring about several conformational and enzymatic changes in macrophages. Exogenous foreign bodies and released endogenous unexposed substances are frequent causes of giant cell transformation of macrophages. These include hemorrhages (red cells and plasma), cholesterol, keratin, hair; milk secretion, sperms and mucin etc. Sometimes the inciting agent of giant cell transformation of the macrophages is not clearly identified, e.g. sarcoidosis. A cell may enlarge due to enzyme deficiency leading to unprocessable excessive accumulation of endogenous substances e.g. Gaucher's [19] and Neimann-Pick cells containing glucocerebrosidase and sphingomyelin due to corresponding deficiency of glucocerebrosidase and sphingomylinase, respectively. At times congenital malformations and hamartomas may contain large "dysplastic" (malformed) cells, e.g., cortical heterotopias. Tumors, both benign and malignant may contain tumor giant cells, e.g., pheochromocytoma, large cell anaplastic carcinoma of thyroid [20, 21] and Hodgkin lymphoma; the last may be due to viral induction [22].

The giant cells in GCTB appear to be transformed circulating monocytes, many if not all of which have converted into active osteoclasts (see below). The stromal cells in GCTB appear to be activated fibroblasts. Like giant cells, stromal cells may become
activated from hemorrhage-induced release of red cells and plasma proteins into the matrix. As there is increased telomerase activity in rapidly proliferating normal tissue, e.g. epidermis, endometrium and lymphocytes, increased telomerase activity and prevention of shortening of the telomeres is understandable in rapidly proliferating giant cells and may not necessarily indicate a true neoplastic nature.

**Hemorrhage**

Hemorrhage in different tissues may give rise to various manifestations [23-27]. These include edema, fibroblast activation and fibrosis if hemorrhage persisted, macrophage and multinucleated giant cells with ingested red blood cells, hemosiderin and cholesterol clefts, xanthomatous cells, and tissue destruction such as necrosis, cystic formation, dystrophic calcification and ossification. To various degrees, these pathological changes can be seen in the different pathological conditions, such as adenomatous goiter, brown tumor in hyperparathyroidism and GCTB (Figure 3).

Intact, fragmented and degenerated red cells, hemoglobin, hemosiderin and cholesterol derived from hemorrhage are invariably seen in the cytoplasm of the giant cells of the GCTB (Figure 4A). The giant cells are particularly prominent around the areas of hemorrhage as if they are sipping and siphoning blood from these areas (Figure 4B). Adjacent to the foci of hemorrhage, dilated vessels (Figure 4B) and markedly edematous stroma are frequently encountered. As the hemorrhage usually causes tissue damage and necrosis, it is conceivable that some trabecular bone matrix is exposed to the giant cells (Figures 4C and 4D). This may induce changes of physical conformation, gene expression and enzymatic activities in giant cells transforming them into osteoclasts (Figures 4E and 4F). Significant configuration modulation and modification and new gene expression perhaps occur. Rapid,
sustained and significant division of the nuclei may require enhanced telomerase activity.

**From Giant Cells to Osteoclasts**

There are many morphological and cytochemical similarities between giant cells of GCTB and osteoclasts [28]. These include abundant calcitonin receptors [29], response to calcitonin with a rise in cyclic adenosine monophosphate [30], capability of forming resorption pits on bone slices in a manner identical to that of osteoclasts [31], ruffled borders and clear zones, ultrastructural features that are characteristic of the osteoclast, have been seen on these giant
cells forming resorption lacunae [32] and positive for tartrate-resistant acid phosphatase [33]. In addition, the giant cells of GCTB express the same macrophage-associated antigen profile as the osteoclasts [34, 35], a feature particularly useful in distinguishing the giant cells of GCTB from giant cells in other giant-cell-rich tumors and tumor-like lesions of bone, such as non-ossifying fibroma and aneurysmal bone cyst [36]. The only other tumor in which giant cells have been reported to show an identical osteoclast-like phenotype is giant-cell granuloma of the jaw [37]. The commonly employed technique of cell culture on bone slices to determine evidence of lacunar resorption was first carried out with use of cells isolated from a giant-cell tumor of bone [38].

Based on the above facts and several experiments in contrary to the previous beliefs [39], it is now generally accepted that osteoclasts are formed by circulating monocytes [40-50].

Parathormone in GCTB

Parathormone plays a significant role in the differentiation of immature precursors to mature osteoclasts as well as their conversion to multinucleated cells [51-56]. Prostaglandin E\(_2\) also has been reported to be involved in the stimulatory effects of other hormones and cytokines [46, 54, 57-60].

Parathormone has several known effects on osteoclasts. These include proliferation of osteoclast, formation of osteoclast precursors from monocytes as well as differentiation of osteoclast precursors to functional osteoclasts [61, 62]. However these studies do not explain the effect of frequent hemorrhage. In fact, many cytokines and other active chemical mediators are plasma and/or red cell-derived. The hemorrhages may result in neovascularization to support increased osteoclastic activity. The newly laid vessels easily rupture and bleed being too fragile and weak as seen in adenomatous goiter.

Stromal Cells

It has been proposed that the stromal cells of GCTB release chemokines such as macrophage chemo-attractant protein 1 and interleukin-8 [63, 64], which could further recruit more monocytes into the tumor, which then can transform into mature osteoclasts.

It seems quite likely that the hemorrhage may stimulate and activate the stromal cells to secrete these chemokines. On the other hand it is also possible that some of the chemokines attributed to stromal cells might have derived from plasma itself. Within GCTB samples, expression of high levels of mRNA encoding osteoclast differentiation and activation factor (ODF) and its receptor RANK, as well as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) was found. In a small series of tumors, a relationship between expression of the relative levels of ODF and TRAIL, in terms of the corresponding level of osteoprotegerin (OPG), with the degree of bone lysis by these tumors in vivo has been observed. The synthesis of interleukin-6 and interleukin-11, both products of stromal cells and osteoblasts, is stimulated by parathormone, 1, 25-dihydroxyvitamin D\(_3\), and parathormone-related peptide [65].

Local Environment

Localized abnormal resorption of bone may result from a variety of causes including neoplasm, inflammatory lesion, parathormone-induced changes, abnormal collagen matrix, dilated vessels and hemorrhage.

Neoplastic and inflammatory cells release numerous cytokines, prostaglandins, and other local factors that enhance the bone-resorptive activity of mature osteoclasts [66-68]. This effect is mediated indirectly by osteoblasts. They also release proteases that degrade organic matrix covering osseous surfaces, expose mineralized matrix, and thus activate osteoclastic bone resorption [69, 70]. The release of prostaglandins, cytokines, and growth factors by inflammatory and tumor cells may also act on osteoblasts and stromal cells to regulate the formation of osteoclasts from monocytes.

Macrophages are a major component of the host cellular response to neoplastic and inflammatory lesions in bone [71-74]. Tumor-associated macrophages derived from primary carcinomas of the lung in humans and of the breast in mice [35, 75, 76], as well as inflammatory foreign-body macrophages derived from granulomas induced by the wear particles of implanted biomaterials [77, 78], have all been shown to be capable of

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osteoclastic differentiation. The tissue macrophages are heterogeneous in terms of their morphology, function, immunophenotype, and enzyme histochemistry [79]. This heterogeneity is also reflected in their proliferative potential; approximately 5% of tissue macrophages are capable of further division [80]. Rapid extensive osteolysis is seen in association with a pronounced foreign-body macrophage response to the formation of numerous wear particles from implanted biomaterials [81, 82]. Inflammatory granulomas are known to contain an increased number of such phagocytes with proliferative potential [83].

Vascular Factor

Several workers have suspected angiogenic nature of the tumor which had prompted some workers to try calcitonin [84, 85] because this hormone inhibits bony resorption and there is a presumption that the osteoclast plays a role in this tumor. Similarly, Interferon alfa-2a is an angiogenesis inhibitor. It slows endothelial migration [86] and inhibits angiogenesis in vivo [87]. Interferon is known to inhibit mRNA and protein production of the two known angiogenic factors, β-FGF and interleukin-8 [88]. There are reports of using interferon to control giant cell tumors of the long bones [89, 90]. VEGF and MMP-9 expression in osteolytic lesions of bone correlates well with the extent of bone destruction and local recurrence [91].

The questions had been asked that how stromal cells of GCTB recruit osteoclast precursors. It is suggested that stromal derived factor-1 (SDF-1) is one of the significant chemoattractant factors involved in the recruitment of hematopoietic osteoclast precursor cells (monocytes) during tumor-induced osteoclastogenesis [12]. Our proposal is that hemorrhage provides fresh monocytes as well as plasma proteins. The plasma proteins stimulate both homed monocytes and stromal cells. The activated stromal cells in turn may facilitate conversion of giant cells into active osteoclasts (Figure 5).

Genetic Abnormalities

The lack of telomere shortening, increased telomerase activity and karyotypic aberrations are generally considered “proof” of neoplastic nature of a neoplasm. In one study, telomeric fusion was the most striking random chromosomal abnormality detected in 6 of 20
GCTB cases which raised the possibility of being useful in predicting the biologic behavior of these neoplasms [92]. In another study, the activity varied and was less than that observed in HeLa [93]. One study concluded that microsatellite instability does not appear to play a role in the tumorigenesis of GCTB [94]. Even normal rapidly proliferating tissue, e.g. endometrium, epidermis and lymphocytes have been shown to contain heightened telomerase activity. On the other hand, several non-neoplastic bone conditions, e.g. ABC, fibrous histiocytic reaction and osteochondroma (exostosis) have been shown to contain high telomerase activity. The giant cells are known for their rapid proliferation and multiplication of nuclei and hence increased telomerase activity and fusion of telomere will be rather expected in these conditions and do not necessarily indicate neoplastic nature of the GCTB. Telomere length reduction was observed in 69% of the GCTB [95]. In one study, 3 of the 5 cases showed telomeric fusions of 11pter. These findings support the concept that telomeric instability is responsible for a large degree of intratumor heterogeneity and serves as a precursor lesion to subsequent clonal structural aberrations of chromosome 11 in GCTB [96]. Other studies also presented similar findings [97, 98].

GCTB and ABC: Are They Related?

ABC is considered a non-neoplastic expansile lesion consisting of blood-filled spaces separated by connective tissue septa containing bone or osteoid and osteoclast giant cells. It arises in 1/3rd cases of preexisting bone tumor, suggesting that the lesion arises in abnormal osseous matrix. It may arise in GCTB, chondroblastoma, chondromyxoid fibroma, osteoblastoma, or fibrous dysplasia. Less often it may arise from osteosarcoma, chondrosarcoma, and hemangioendothelioma [99, 100]. Recently various studies have claimed that chromosomes 16q22 and 17p11-13 are nonrandomly involved in at least some ABCs. This was not found in any of 17 secondary ABC associated with GCTB, chondroblastoma, osteoblastoma and fibrous dysplasia [101]. Similarly, among 38 patients with ABC, clonal chromosomal abnormalities were seen in 12 specimens. Karyotypic anomalies of 17p, including a complex translocation and inversion, were identified in eight of these 12 specimens [102]. The crucial question is whether these aberrations can be taken as a substantial proof for the true neoplasm nature of ABC or these can be seen in reactive rapid proliferation of various cells particularly endothelial cells and mesenchymal cells. It would be rather unwise to separate ABCs into primary versus secondary as it will be very hard to draw the lines.

The exact etiology of ABC is unknown. In one case series, antibody to factor 8 stained the edge of ABC cavities in almost all cases, and antibodies to VEGF-C, GLUT-1, and smooth muscle actin stained the edge of the cavities in approximately half the cases. Antibodies to D2-40 and CD34 also stained the edge of the cavities in some cases. These results suggest that the cavities in ABCs are related to vasculature and support the theory that vascular injury may be important in the pathogenesis of ABC [103].

Microcysts and blood-filled spaces, similar to those seen in aneurysmal bone cysts can be seen in central giant cell granulomas, fibrous dysplasia, ossifying and cementifying fibromas, Paget's disease of bone, osteosarcomas and rarely in fibrosarcoma. It is postulated that the initiating process of the aneurysmal bone cyst is the microcyst, which forms as a result of intercellular edema in a primary lesion with loose, unsupported stroma. Rupture of vessels into the microcysts introduces blood under haemodynamic pressure. With little resistance provided by the stroma, the blood spaces resorb the surrounding bone and lift the periosteum, which produces a thin shell of new bone [104].

We believe that ABCs are formed due to direct or indirect (e.g. poor matrix support) vascular weakness. This could be due to direct endothelial damage or could be indirectly due to defective collagen matrix of vessels or surrounding parenchyma or both. Lack of sufficient support always leads to aneurysmal dilatation as seen in adult polycystic kidney where vessels in addition to tubules are dilated giving rise to frequent cyst formation, hemorrhage and loose yet pressurizing matrix. Similar telangiectatic vessels can be seen in prolonged steroid treatment in skin biopsies. Vitamin C deficiency-induced vascular collagen weakness leads to frequent sub-periosteal hemorrhage. The thin-walled vessels are markedly dilated over time and may give rise to balloon-like swellings in the bone, i.e.
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aneurysmal bone cysts. These fragile vessels are easy to rupture. The extravasated RBCs and plasma stimulate fibroblast proliferation. Some of the monocytes start engulfing large number of red blood cells. These can be seen in the pictures of the most of the reported cases of GCTB. We have seen several cases of GCTB and never failed to see the intact, fragmented and partially dissolved red blood cells ingested by the giant cells. As some of these monocytes convert into active osteoclasts, bone resorption ensues. Hence a classical GCTB may emerge. With passing time, it may be difficult to identify thin-walled blood vessels. However, a diligent search will not fail in finding some dilated thin-walled vessels. Depending upon the relative quantity of giant cells, aneurysmally dilated vessels and fibrohistiocytes, the tumor may appear as GCTB, ABC or fibrous histiocytoma of bone, respectively (Figure 3).

Many times the histopathological findings may be a mixture of all components and the differential diagnosis of GCTB not surprisingly would include central giant cell granuloma, ABC and osteitis fibrosa cystica (brown tumor) [105]. As very few GCTBs are malignant, i.e. the malignant tumor with giant cells reaction, multiple fine needle aspiration cytology (FNAC) from different areas would rule out such possibility. FNAC brings out a large number of giant cells as well as stromal cells. The malignant cells from osseous lesions are easily and readily picked up by FNAC [106-110]. FNAC thus may play an important role in conservative management of this lesion.

Malignant GCTB?

Although GCTB had been divided into benign, border line and malignant, we believe that the malignant lesions represent other malignant tumors, e.g. osteogenic sarcoma from the very beginning with prominent areas of hemorrhage and giant cell formation. In almost all these instances, the original malignant tumor is overshadowed by the giant cell reaction and missed by the pathologist. We agree with Rosai [7] that the presence of giant cells should prompt a diligent search for atypical cells in order not to miss the malignant lesion, e.g. osteogenic sarcoma if present.

Conclusion

Based on review of the literature and our own observations, GCTB is not a true neoplastic lesion. Like many other giant cell-containing conditions, these appear to be a local reactive condition i.e. non-neoplastic tumor secondary to hemorrhage. The hemorrhage could be in turn due to defective collagen in the matrix and/or in the vessel wall. Defective vessels and hemorrhage in other conditions e.g. parathormone induced brown tumors could have similar microscopic appearance. Defective collagen also may cause aneurysmal dilatation of the vessels leading to ABC. Fibrosis is a natural general sequel of long standing edema and hemorrhage; hence some hemorrhagic foci may lead to fibrohistiocytic foci. Hemorrhagic foci through hormonal and other chemical influence give rise to similar lesions, e.g. brown tumor of hyperparathyroidism. We conclude that GTCB is a non-neoplastic reactive condition based primarily on significant intraosseous hemorrhage which in turn could be due to poor local osseous matrix support to the vessels. Various karyotypic and telomerase related findings could be a reflection of physiological proliferation of giant cells and nuclei within giant cells as well various matrix cells under influence of exuded plasma. A genetic predisposition obviously at different levels i.e. osseous matrix and tendency to form copious giant cells can not be ruled out. As defective vessels and hemorrhage can be controlled by newer modalities such as laser and hormone therapies, further studies are requires for a conservative management of these lesions.

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