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ORIGINAL ARTICLE

CD10 and CD138 can be expressed in giant cell tumor of bone: An immunohistochemical study

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ABSTRACT

Giant cell tumor of bone (GCTB) is a primary bone neoplasm which is characterized by the presence of mononuclear cells (MCs) and osteoclast-like multinucleated giant cells (MNGCs). Up to our knowledge, CD10 immunoreactivity in GCTB has not yet been studied, and only one study touched on CD138 immunoreactivity in GCTB. The objective of this study is to investigate the immunoreactivity of CD10 and CD138 in GCTB. We offer a discussion of our findings in the context of the differential diagnosis, particularly in small biopsy material. We retrieved and reviewed 15 well-documented cases of GCTB from January 2008 to December 2014. Well-controlled standard immunohistochemical satins were performed on these cases for CD10 and CD138 and few other selected antibodies. Immunoreactivity for CD10 was membranous and was found in 14 (93%) cases. This immunoreactivity was found only in the MCs, whereas the MNGC were all negative. CD138 showed variable positivity in 11 (73%) while 4 (37%) were completely negative. Similar to CD10, staining for CD138 was only seen in the MC; however, the immunoreactivity was predominantly concentrated in the peri-vascular areas. Most of GCTB cases can show variable immunoreactivity for CD10 and CD138. The aforementioned immune-expression raise the possibility of a role in the pathogenesis of GCTB. Paying attention to this immunoreactivity is recommended when considering the clinical and radiological differential diagnosis, especially in small biopsy specimens.

Key words: CD10, CD138, giant cell tumor of bone

INTRODUCTION

Giant cell tumor of bone (GCTB) is relatively uncommon primary tumor of bone accounting for approximately 5% of all primary bone tumors and 20% of benign primary bone tumors.[1,2] This neoplasm usually affects both males and females in the third or fourth decade of life with a slight female predominance and rare occurrence in children below the age of 10 or beyond the age of 45.[3] These tumors typically affect the epiphysis of long tubular bones, most commonly distal femur, proximal tibia, distal radius, and proximal humerus.[1] On clinical grounds, GCTB commonly presents with localized pain and swelling with the limitation of joint movements, however, in rare occasions, the patient may present with a pathological fracture.[2] The plain X-ray of GCTB commonly shows lytic, eccentric and expanding appearance while the computed tomography scan and magnetic resonance imaging will reveal a more accurate localization and extent of the lesion.[1] GCTB is considered a benign, but locally aggressive neoplasm with a relatively high incidence of recurrence but with rare distant metastasis.[1,2] The treatment of choice is complete local excision or segmental resection, however, and despite

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its controversy, additional use of postcurettage adjuvant therapy can be utilized in few unusual cases.[3]

Histologically, GCTB is characterized by mixture of osteoclast-like multinucleated giant cells (MNGCs) thought to arise from a histiocytic lineage and stromal mononuclear cells (MCs). In most cases, the diagnosis depends on the clinical and radiological appearance combined with the aforementioned histopathological features. In general and for practical purposes, no additional immunohistochemical studies are needed to confirm the diagnosis.[1] However, in some cases, the clinical and radiological picture may raise a short list of serious differential diagnosis including sarcomas, carcinomas, and hematologic malignancies. In these situations, immunohistochemical stains can be utilized to help resolve these questions and confirm the final diagnosis. The latter is of critical importance when the pathologist is dealing with either small core biopsy or fine-needle aspiration material.[4-6]

We encountered a patient who was 62-year-old with the previous history of renal cell carcinoma who developed a lytic bone lesion in the proximal femur where a fine needle aspiration immediately followed by a small core needle biopsy revealed numerous MNGC. Because of the patient older age, unusual osseous location and the lytic nature of the lesion, the clinician and the radiologist insisted to rule out metastatic carcinoma and plasma cell myeloma. Interestingly, these cells were found to be immunoreactive for CD10 and CD138. However, because of the distribution of these cells, the diagnosis of GCTB was favored. The lesion was completely curetted and the final histopathological diagnosis was GCTB.

CD10, a common acute lymphoblastic leukemia antigen (CALLA) is the zinc metalloprotease, neutral endopeptidase (NEP) 24.11 (NEP, "enkephalinase") which is expressed on early lymphoid progenitors and neutrophils.[7-9] It is also expressed in several mesenchymal, lymphocytic and epithelial tumors including endometrial stromal tumors, follicular lymphoma, Burkitt lymphoma, renal cell carcinoma, and solid-pseudopapillary tumor of the pancreas.[7-9] However, after reviewing the English language literature and up to the best of our knowledge, its expression in GCTB has not yet been evaluated.

CD138 (syndecan-1) is a cell surface proteoglycan which is considered a sensitive and specific marker for plasmacytic differentiation in hematological disorders.[10,11] However, it has been shown that it can be expressed in nonhematologic tumors including breast carcinoma, hepatocellular carcinoma, plasmacytoid transitional cell carcinoma of the urinary bladder, renal cell carcinoma, and papillary thyroid carcinoma.[10] On the other hand, after reviewing the English literature and up to the best of our knowledge, only one study touched on the immunoreactivity of GCTB for CD138.[11]

The aim of this study was to evaluate the immunohistochemical expression of CD10 and CD138 in GCTB and evaluate their role in the differential diagnosis. Moreover, the study included GCTB immunoreactivity for CD68, epithelial membrane antigen (EMA), AE1/AE3, Ki-67, cyclin D1, and CD117.

METHODS

After approval from the internal review board, we retrieved and reviewed 15 well-documented cases of primary GCTB from three institutions in the Eastern Province of Saudi Arabia (King Fahad Specialist Hospital-Dammam, John Hopkins Aramco Health Care and Saad Specialist Hospital) from January 2008 to December 2014. All the cases were reviewed, and none was reclassified. No cases of brown tumor of bone were included in this study. Well-controlled standard immunohistochemical satins were performed on these cases for CD10, CD138, EMA, AE1/AE3, Ki-67, cyclin D1, CD117, and CD68 [Table 1].

RESULTS

There were 8 males and 7 females with an average age of 29 years (range 16–46 years). Positivity for CD10 was

Table 1: The antibodies list details

Antibody	Clone	Company	Incubation time (min)	Concentration	Antigen retrieval	Origin
Ki-67	30-9	Ventana, Tucson, USA	32	RTU	CC1STD	Rabbit
CD138	MI15	Dako, Glostrup, Denmark	20	RTU	HIER (Flex High pH)	Mouse
Cyclin D1	SP4-R	Ventana, Tucson, USA	32	RTU	CC1 STD	Rabbit
Cytokeratin	AE1/AE3 and PCK26	Ventana, Tucson, USA	16	RTU	Protease 1-4 min	Mouse
CD68	KP-1	Ventana, Tucson, USA	32	RTU	CC1 STD	Mouse
Epithelial membrane antigen	E29	Ventana, Tucson, USA	16	RTU	CC1MILD	Mouse
CD10	56C6	Ventana, Tucson, USA	32	RTU	CC1STD	Rabbit
CD117	9.7	Ventana, Tucson, USA	32	RTU	CC1STD	Rabbit

RTU: Ready to use, CC1STD: Standard cell conditioning, CC1MILD: Mild cell conditioning, HIER (flex high pH): Heat induced epitope retrieval using high pH buffer

found in 14 (93%) cases, where the immunoreactivity was found only in the MCs while the MNGC were all negative [Figure 1]. The CD10 staining pattern was predominantly membranous. Of these, 8 (53%) showed strong diffuse immunoreactivity and 6 (40%) showed focal and variable staining intensity [Figure 2]. CD138 showed variable positivity in 11 (73%), whereas 4 (37%) were completely negative. After comparing the CD138 positive and negative cases, there was no morphological difference noted. In one of these cases (7%), the immunoreactivity was diffuse and strong [Figure 3]. Similar to CD10, staining for CD138 was only seen in the MC component but with a trend of stronger staining in the peri-vascular areas [Figure 4]. The staining pattern of CD138 was membranous and occasionally cytoplasmic with dot-like appearance [Figure 3]. In one case, the MNGC showed obvious cytoplasmic positivity for CD138. All cases showed positivity for CD68 where MNGC showed strong and diffuse staining and the MC cells were obviously weaker and more focal [Figure 5]. The proliferative index Ki-67 immunoreactivity on the nuclei of these cases was seen in the range from 3% to 20% and was <2% in one case which showed foamy ancient change. Ki-67 staining was only seen in the nuclei of the MC cells and was negative in the MNGC [Figure 6]. Cyclin D1was strongly and diffusely positive in the nuclei of MNGC but weak and focal in MC [Figure 7]. None of the cases showed reactivity for CD117, AE1/3, or EMA [Table 2]. We also performed CD10 and CD138 in 15 cases of giant cell tumor of tendon sheath and 5 cases of the giant cell containing aneurysmal bone cyst, and none showed immunoreactivity.

DISCUSSION

CD10 is a 100 kDa cell surface glycoprotein and was initially described as a tumor-associated antigen in acute lymphoblastic leukemia, hence the name (CALLA). It is also expressed in other lymphoid malignancies with an

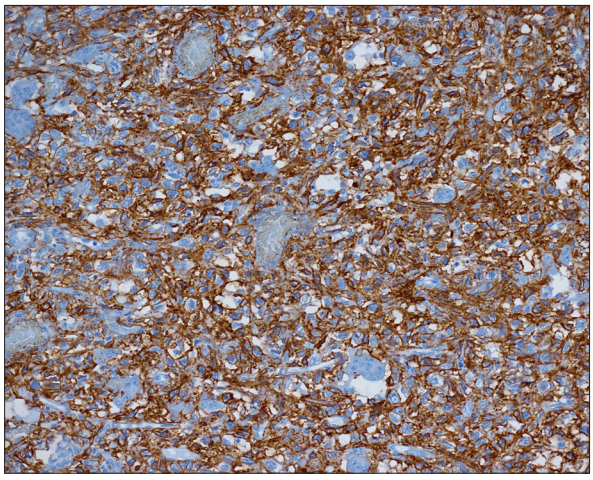

Figure 1: (Patient #9): Low-power view of CD10 showing diffuse membranous immunoreactivity of mononuclear cells while sparing multinucleated giant cells

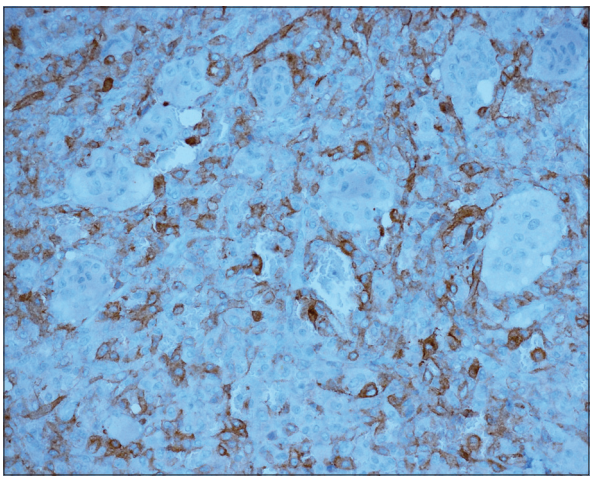

Figure 2: (Patient #2): High-power view showing focal and variable membranous immunoreactivity of CD10 in mononuclear cells

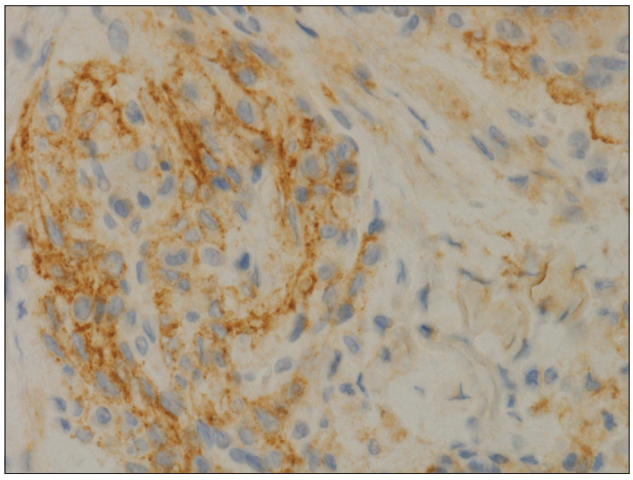

Figure 3: (Patient #7): High-power view of CD138 showing the diffuse and dot-like background immunoreactivity

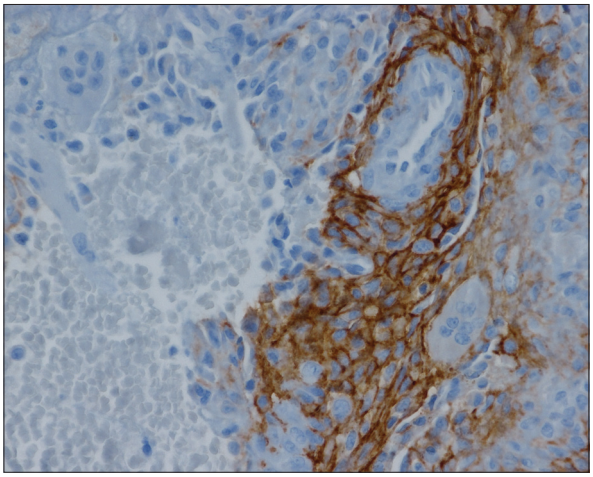

Figure 4: (Patient #5): Medium-power view exhibiting CD138 membranous immunostaining of mononuclear cells. The staining is obviously concentrated in the peri-vascular areas

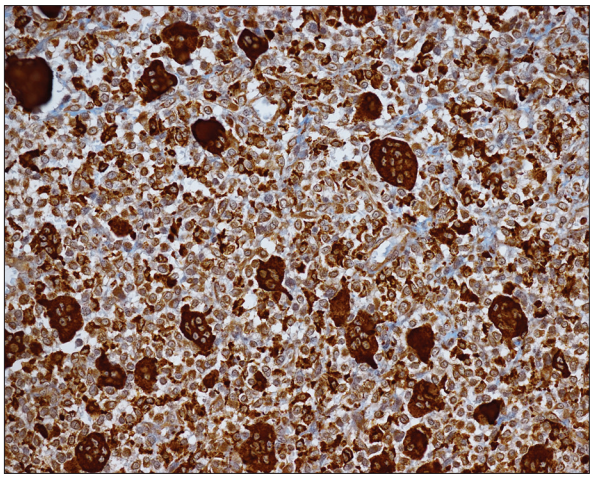

Figure 5: (Patient #12): Low-power view showing CD68 strong and diffuse immunostaining of multinucleated giant cells in contrast to weak and focal staining of mononuclear cells. The staining is predominantly cytoplasmic

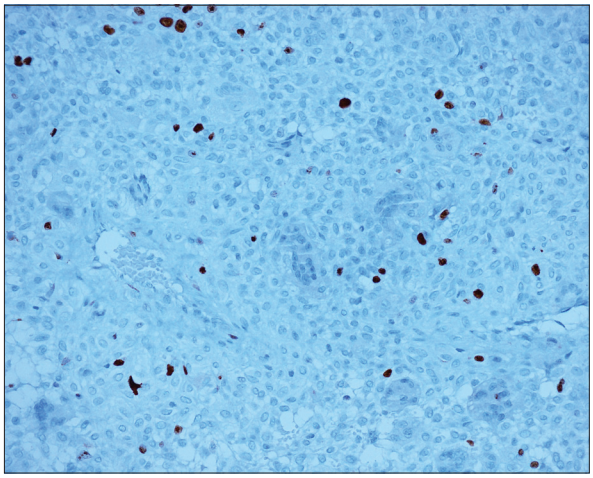

Figure 6: (Patient #15): High-power view of Ki-67 showing nuclear immunoreactivity only in mononuclear cells in approximately 3–5% of the cells

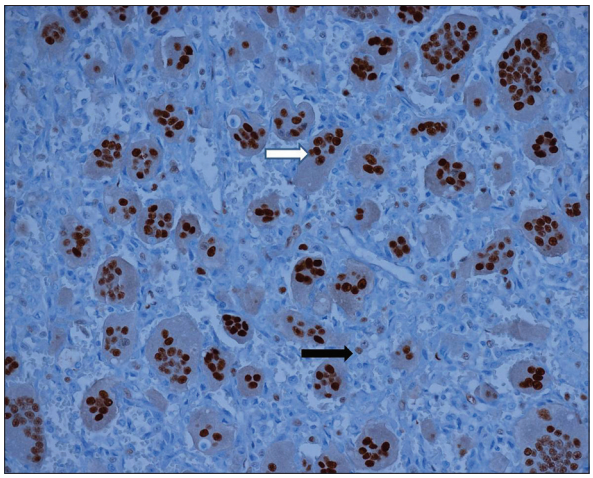

Figure 7: (Patient #14): Medium-power view showing cyclin D1 strong nuclear immunostaining of multinucleated giant cells (white arrow), and weak focal staining of mononuclear cells (black arrow)

immature phenotype, early lymphoid progenitors, and mature polymorphonuclear leukocytes. This expression profile suggested a role in hematopoietic differentiation. Molecular studies of the nucleotide sequence of CD10 showed that it is identical to that of the zinc metalloprotease, a NEP 24.11 (NEP, "enkephalinase"). NEP is a cell membrane-associated enzyme that cleaves peptide bonds on the amino side of hydrophobic amino acid. Biologically active peptides such as met-enkephalin, formyl-met-leu-phe and substance *P* induce the migration and aggregation of neutrophils, and they are hydrolyzed by CD10/NEP suggesting a role in controlling the response of inflammatory peptides. However, CD10 has also been demonstrated in nonhematopoietic normal tissue as well as nonhematopoietic tumors. Such reactivity was demonstrated in the genitourinary and gastrointestinal tissue where it usually exhibits strong Golgi, apical, and luminal pattern positivity. The aforementioned finding suggested a role of CD10 in the secretory process of tumors arising from these organs. In this study, CD10 was positive in 93% (n = 14) of GCTB cases. Interestingly, it is expressed only in MC with 53% (n = 8) cases showed strong diffuse reactivity with an only membranous pattern of staining. Up to our knowledge and after reviewing the English literature, this is the first study addressing the immunoreactivity of GCTB for CD10, and it is believed that the lack of such studies may be explained by the fact that CD10 is not a usual immunohistochemical markers for GCTB. Although the origin of the neoplastic cells in GCTB is the MCs rather than the MNGCs, there are still strong debate about the true nature and origin of these neoplastic cells. Multiple studies had suggested that these mononuclear neoplastic cells express multiple osteoblastic associated antigens supporting an origin from osteoblasts or an osteoblastic lineage. In addition, since CD10/NEP was shown to be expressed in osteoblasts and cultured osteoblast-like cells, we strongly believe that CD10 expression in the mononuclear neoplastic cells of GCTB provides additional evidence supporting the osteoblastic origin of these cells.[12,13]

Since the differential diagnosis of unusual lytic bone lesions in the appropriate clinical settings may include renal cell carcinoma, which is known to be CD10 immunoreactive, paying attention to this immunoreactivity is warranted to include GCTB in the differential diagnosis of these cases. This phenomenon may be very important in particular when we are dealing with small amount of material procured either by small core biopsies or fine-needle aspiration.[6]

CD138 (syndecan-1) is a transmembrane heparin sulfate cell surface proteoglycan that mediates cellular functions such as cell-to-cell adhesion, cell-matrix interaction, and cell proliferation and differentiation.[11] It is a highly sensitive and specific marker for plasmacytic differentiation. However, it

Table 2: Patients details and immunostains results

Case	Age (year)/ sex	Site	CD10		CD138		CD68		Ki-67		Cyclin D1		AE1/AE3, EMA and CD117	
			MC	MNGC	MC	MNGC	MC	MNGC	MC (%)	MNGC	MC	MNGC	MC	MNGC
1	34/male	Proximal tibia	D+++	0	+ PFPV mem	0	+	+++	3-10	0	+	++	0	0
2	35/male	Proximal tibia	F+	0	++ PFPV mem	0	+	+++	3-10	0	+	++	0	0
3	22/female	Radius	D+++	0	+ PFPV mem	++ cytoplasmic	+	+++	3-10	0	+	+++	0	0
4	29/female	Ulna	D+++	0	++ PFPV mem	0	+	+++	3-10	0	+	+++	0	0
5	32/male	Distal humerus	F+	0	+ PFPV mem	0	+	+++	3-10	0	+	++	0	0
6	35/male	Tibia	D+++	0	+ PFPV mem	0	+	+++	10-20	0	+	++	0	0
7	27/female	Phalanx	F+	0	D +++ mem, dotlike	0	+	+++	3-10	0	+	+++	0	0
8	46/male	Proximal tibia	D+++	0	+ PFPV	0	+	+++	3-10	0	0	++	0	0
9	45/female	Proximal fibula	D+++	0	0	0	+	+++	<2	0	+	++	0	0
10	19/female	Tibia	F+	0	++ PFPV mem, dotlike	0	+	+++	2-7	0	+	++	0	0
11	22/female	Radius	F+	0	0	0	+	+++	5-20	0	+	+++	0	0
12	17/female	Distal femur	D+++	0	++ PFPV, dotlike	0	+	+++	5-20	0	+	++	0	0
13	16/male	Maxillary sinus	F+	0	0	0	+	+++	3-10	0	+	++	0	0
14	43/male	Cervical verterbrae	D+++	0	0	0	+	+++	10-20	0	+	+++	0	0
15	16/male	Skull, nose	F+	0	+ PFPV mem	0	+	+++	3-5	0	+	++	0	0

+: Weak staining, ++: Intermediate intensity staining, +++: Intense staining, 0: No staining, MC: Mononuclear cell, MNGC: Multinucleated giant cell, D: Diffuse, F: Focal, PFPV: Positive, focal and perivascular, Mem: Membranous staining

is readily detected in a limited number of epithelial and mesenchymal tumors. In this study, 73% showed focal positive immunohistochemical reactivity in GCTB. The staining pattern is membranous and occasionally dot-like, and it is expressed only in MC (except in one case) with more intensity in cells close to blood vessels [Figure 4]. Recently, Nunez *et al*. studied the expression of CD138 in multiple bone forming tumors.[11] Of the 12 cases of GCTB in their series, no expression of CD138 was found. We looked at the source and the clone of an antibody that they used, and we compared it with ours, interestingly the antibody clone and the manufacturer was the same. We repeated the CD138 stain in our cases again, and the results were the same. Therefore, we can only speculate that such an expression is maybe an artifact and may represent a spill-over from blood vessels. Hence the immunoreactivity was predominantly peri-vascular. Therefore and regardless of its nature, CD138 expression can occur in GCTB and in small biopsies and fine-needle aspiration material and its expression should be interpreted with extreme caution.

Cyclin D1 is a cell cycle regulating protein.[14] In our study, it showed strong and diffuse reactivity in the nuclei of MNGC but weak and focal staining in MC. Similar results were described by Werner in 2006.[15] He explained the immunoreactivity for cyclin D1 and its relationship with another protein (p21) as an evidence of its reactive rather than neoplastic nature.[15] Three years later, Matsubayashi *et al*. demonstrated similar results of cyclin D1 in MNGC and they suggested that it may play a role in MNGC formation instead of promoting cell proliferation during tumorigenesis.[14]

CD117 (c-kit) was not expressed in any of our cases, which was similar to the results published by Ramos *et al*.[16]

Since there is agreement that the MNGC of GCTB are of histiocytic origin and as our study showed, expression of CD68 by these cells was not surprising.[17]

The Ki-67 antigen is a human nuclear protein used as a marker for cellular proliferation. Ki-67 proliferation index in our study was ranging from 5% to 20% except in one case which was <2%. It was positive only in MC confirming its proliferative nature. However, Ismail *et al*. studied the Ki-67 proliferative activity concluding that it may not be a useful marker to predict local recurrence and lung metastasis in Stage 3 GCTB.[18]

Since there is no evidence of the epithelial origin of these cells, it was not surprising that the epithelial markers (AE1/AE3 and EMA) were found to be completely negative in our series.

CONCLUSION

Most of GCTB cases can show variable immunoreactivity for CD10 and CD138, where only the neoplastic MC are positive. The aforementioned relatively high expression may raise the possibility of its role in the pathogenesis of GCTB.

However, we need to emphasize that paying attention to this immunoreactivity is recommended when considering the clinical and radiological differential diagnosis, especially in small biopsy specimens.

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Conflicts of interest

There are no conflicts of interest.

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