Multicentric giant cell tumour of bone

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Although giant cell tumour (GCT) is seen quite frequently, multicentric giant cell tumour (MCGCT) is a rare entity occurring in less than 1% of patients with GCT. The pathogenesis of MCGCT is debated ; various mechanisms have been postulated, including contiguous spread, iatrogenic tumour cell seeding, benign metastasis, malignant transformation and *de novo* formation. A literature review revealed 101 cases of MCGCT reported worldwide, of which we could trace and review 83 cases. We noted that MCGCT, unlike the solitary GCT, more frequently involves the short bones of the hand and feet and is commoner in the meta-diaphyseal region of long bones. The present literature review noted a higher incidence in females and skeletally immature patients (21%). Individual lesions in a patient with MCGCT are radiologically and histologically indistinguishable from the solitary GCT. In our review we noted 42 recurrences in 157 lesions (26%), thus negating the commonly held point of view that MCGCT was clinically more aggressive. Four lung metastases and two histologically malignant lesions were found. The literature does not define the exact time period beyond which a lesion can be classified as metachronous ; however a significant number of the subsequent lesions occur within 2-3 years of the index lesion. We recommend from our review, that with the present state of knowledge, special care should be taken in cases with primary meta-diaphyseal lesions, GCTs seen at atypical locations, and in females of younger age group, to ensure that multicentricity is picked up earlier.

Keywords : giant cell tumour ; multicentric.

INTRODUCTION

Giant cell tumour (GCT) of bone is a benign aggressive tumour with features of frequent local recurrences and potential for metastasis and malignant transformation (*13, 16, 42, 48*). In its most standard presentation GCT is a solitary neoplasm, growing eccentrically in the epi-metaphysis of long bones of mature young adults (most often in the second to fourth decade of life) with a male : female ratio of 1:1.5 (*66*). Nearly 50% of the cases occur in the region of the knee, and other frequent sites include the distal radius, proximal humerus and fibula, and the pelvic bones (*6, 13, 50, 66, 69*). Atypical locations are rare, and the tumour diagnosis in these circumstances is often confusing. Historically 80% of GCTs have a benign course, with reported local rates of recurrence ranging between 20-50%, most of which are linked to treatment protocols employed. About 10% undergo malignant transformation at recurrence and 1-4% have pulmonary metastasis, even in cases with established benign histopathology (*66*).

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Clinically GCT usually presents with non-specific symptoms like local swelling, pain and warmth. Common radiological features are a lytic lesion, growing eccentrically with bone expansion and cortical thinning. In advanced stages there may be a cortical break (3, 9, 23, 52, 66).

Multicentric giant cell tumour (MCGCT) is an infrequently encountered lesion, where more than one lesion is seen in a patient at presentation ; this may be noted either at the same time in different anatomic locations, or at different times at different anatomic locations, where local spread cannot be perceived to have occurred. A lot of confusion exists with the present state of our knowledge regarding incidence, evolution, pathogenesis, prognosis and management options. The present review (using Medline and other data bases, and cross referencing) was designed to evaluate our present understanding of this complex problem.

INCIDENCE

The available literature reports that solitary GCT accounts for 4-5% of primary bone tumours in the West and 20-30% of primary bone tumours in South East Asia (16, 23, 48, 64). This higher incidence of GCT in our region cannot be satisfactorily explained. Multicentric Giant Cell Tumour (MGCT) nevertheless is a rare entity, with the reported incidence in the literature being less than 1% of all GCTs (13, 16, 19, 41, 42, 48, 63, 70). On reviewing the literature, we found a total of 101 MCGCT cases reported worldwide (tables I, II, III). Series with more than five cases were very few and most of the literature consists of individual case reports (13, 22, 26, 27, 50, 69, 70, 77).

On evaluation of the 101 cases found by the electronic search engines and by cross referencing some non-indexed reports, we noted that 11 of these cases had only a mention of multicentricity, and incomplete data was reported in 21 cases (including 5 in Chinese). Though basic data regarding age, sex and number of lesions was available in 83 cases, sufficient data for a comprehensive review was available in 69 cases (tables I, II, III).

There has been no mention in the literature whether MCGCT is also more common in the south-east Asian region on the pattern of solitary GCT. Our review showed that 11 of the 101 cases were reported from the south-east Asian (Indian and Chinese) region (18, 22, 39, 47, 59, 69), which makes for a relatively lower incidence when compared to solitary GCT.

AGE

The mean age for MCGCT as evaluated by our literature review has been 22.5 years (13, 26, 61, 70, 77). The youngest and eldest cases reported are 9 and 62 years respectively (45, 61). The average age of patients with multicentricity seems to be somewhat lower than in cases of solitary lesions. The peak incidence of solitary GCT is in the third to fifth decades of life, with approximately 80% of patients being older than twenty years of age at the time of diagnosis (9, 14, 15, 42). McInerney and Middlemiss (44) in their series of 135 solitary GCT patients noted that the average age at presentation was 35 years (38 for males and 32 for females). Similarly a large majority of the patients out of the 327 reported by Campanacci et al (9) were in the 20-45 years age group. Other investigators have also noted that patients with MCGCT are considerably younger than those with solitary GCT (52, 61).

SEX INCIDENCE

Of the 82 cases where data for sex was available, there were 38 male and 44 female patients. This preponderance for the female sex has been documented earlier also by various authors for both the solitary (9, 14, 15, 35, 42, 73) and multicentric GCT (3, 13, 52, 61). In 221 solitary GCT patients reported by McDonald et al (42) there were more female (57%) than male patients (43%). Campanacci et al (9) in their series of 327 patients noted an almost equal sex incidence (48.5% males and 51.5% females). Hoch et al (28) noted that out of 17 MCGCT's less than 20 years of age, 13 were female. From our review, we could postulate that female patients presenting with GCT at an age less than 20 years, may have a tendency to develop multicentricity, and should be followed up with care.

Table I. — Clinical details of multicentric giant cell tumours

AUTHOR	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Sybrandy and de la Fuente (65), 1973	1	53	F	3	Nil	ME	1.5 y	2 y	Nil	Nil	Nil	Nil	No recurrence	
Torenberg et al (72), 1975	1	35	M	4	Nil	ME	2 y	4 y	Nil	Nil	Nil	Nil	1	DN
Sim et al (62), 1977	11	20	M	5	Nil	ME	DN	DN	Nil	Nil	Nil	Nil	1	DN
		14	M	9	1	SY	SY	1 y	Nil	2	Nil	Nil	1	DN
		21	M	2	Nil	SY	DN	DN	Nil	Nil	Nil	Nil	Nil	
		21	F	2	Nil	ME	DN	DN	Nil	Nil	Nil	Nil	Nil	
		29	F	2	Nil	ME	DN	DN	Nil	Nil	Nil	Nil	Nil	
		62	F	2	Nil	ME	DN	DN	Nil	Nil	Nil	Nil	Nil	
		24	M	4	Nil	ME	3 y	15 y	Nil	1	Nil	Nil	Nil	
		21	F	2	Nil	ME	DN	DN	Nil	Nil	Nil	Nil	1	DN
		19	F	3	Nil	ME	DN	DN	Nil	Nil	Nil	Nil	Nil	
		21	F	2	Nil	ME	DN	DN	Nil	Nil	Nil	Nil	1	DN
		14	F	3	1	SY	SY	1.5y	Nil	Nil	Nil	Nil	1	DN
Feldman et al (20), 1980	1	35	M	7	Nil	ME	4 y	9 y	Nil	Nil	Nil	Nil	2	1 yr
Peimer et al (52), 1980	5	19	M	3	Nil	DN	DN	DN	Nil	Nil	Nil	Nil	1	DN
		30	M	7	Nil	ME	11 y	DN	Nil	Nil	Nil	Nil	1	DN
		20	F	4	Nil	SY	SY	DN	Nil	Nil	Nil	Nil	2	DN
		17	F	2	Nil	DN	DN	DN	Nil	Nil	Nil	Nil	Nil	
		18	F	2	Nil	SY	DN	DN	Nil	Nil	Nil	Nil	Nil	
Singson et al (61), 1983	1	43	M	10	Nil	ME	4 y	15 y	Nil	1	Nil	Nil	DN	
Duan (19), 1985 CHINESE	5	DATA NOT AVAILABLE												
Wu et al (77), 1986	1	17	F	3	Nil	ME	3 y	12 y	Nil	Nil	Nil	Nil	1	9 yrs
Mittal et al (45), 1987	1	20	M	5	Nil	ME	4 y	7 y	Nil	1	Nil	Nil	No recurrence	
Gaur et al (22), 1987	1	38	F	3	Nil	SY	SY	6 mo	Nil	1	Nil	Nil	No recurrence	
Williams (75), 1989	1	26	M	3	Nil	DN	DN	DN	DN	DN	DN	DN	DN	
Mirra et al (47), 1989	2	24	M	2	DN	DN	DN	DN	DN	DN	DN	DN	DN	
		09	F	2	1	DN	DN	DN	DN	DN	DN	DN	DN	
Madhuri et al (39), 1993	2	23	M	2	Nil	ME	5 y	5 y	Nil	Nil	Nil	Nil	Both	3 y
		27	M	2	Nil	SY	SY	SY	Nil	Nil	Nil	Nil	recurred	7 mo
Hindman et al (27), 1994	5	22	M	5	Nil	ME	3 y	13 y	1	1	Nil	Nil	2	DN
		11	F	9	1	SY	2 m	5 y	Nil	1	3	Nil	DN	
		17	F	2	Nil	ME	4 y	4 y	Nil	1	1	Nil	2	23 yrs
		10	F	2	1	ME	6 y	6 y	Nil	1	1	Nil	DN	
		27	M	2	Nil	ME	15 y	15 y	Nil	Nil	Nil	Nil	Nil	
Bacchini et al (3), 1995	1	29	F	4	Nil	ME	7 y	7 y	Nil	Nil	Nil	Nil	No recurrence	
Gupta et al (24), 1995	1	30	M	4	Nil	SY	SY	SY	Nil	Nil	Nil	Nil	No recurrence	
Cummins et al (13), 1996	5	25	M	9	Nil	SY	SY	20 y	Nil	Nil	Nil	Nil	1	3 yrs
		16	F	3	Nil	ME	3 y	11 y	Nil	Nil	Nil	Nil	Nil	
													Nil	
		22	M	2	Nil	ME	2 y	2 y	Nil	Nil	Nil		Nil	
		14	F	2	1	ME	2 y	2 y	Nil	1	1	Nil	1	6 months
		18	M	6	Nil	ME	4 y	6 y	Nil	1	Nil	Nil	2	2 yrs
Ali (1), 1997	1	30	F	5	Nil	ME	4 m	3 y	Nil	Nil	Nil	Nil	No recurrence	
Taraporvala et al (69), 1997	1	18	M	3	Nil	ME	3 y	9 y	Nil	1	Nil	Nil	No recurrence	
Park et al (51), 1999	1	25	M	3	Nil	ME	10 y	12 y	Nil	Nil	1	Nil	No recurrence	
Sanghvi et al (58), 1999	1	21	F	2	Nil	SY	SY	SY	Nil	Nil	Nil	Nil	No recurrence	
MacDonald et al (10), 2001	1	36	F	2	Nil	ME	10 y	10y	Nil	Nil	Nil	Nil	No recurrence	

Table II. — Hoch *et al* (*28*) - MCGCT clinico pathological analysis of 30 cases

Author	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Hoch *et al* (*28*) 2006	30 (Nine reported earlier)	Average 21 yrs	M/F 1:2	94	8	11 SY	5.3 yrs (in 19 patients with metachronous involvement)	The maximum time in a case was 23 yrs	3	DN	12	2	24 of 94 tumours	2.5 yrs

INDEX TO TABLE I & II
A-   NUMBER OF CASES REPORTED
B-   AGE
C-   MALE/FEMALE
D-   NUMBER OF SITES INVOLVED
E-   NUMBER OF SKELETALLY IMMATURE PATIENTS
F-   SYNCHRONOUS / METACHRONOUS
G-   OCCURRENCE OF THE SECOND LESION AFTER HOW MUCH DURATION FROM THE INDEX LESION
H-   OCCURRENCE OF THE LAST LESION AFTER HOW MUCH DURATION FROM THE INDEX LESION
I-   PRESENCE OF LUNG METASTASES
J-   PRESENCE OF PATHOLOGICAL FRACTURE AT PRESENTATION
K-   NUMBER OF CASES WITH METADIAPHYSEAL LOCATION
L-   NUMBER OF MALIGNANT LESIONS
M-   RECURRENCES
N-   RECURRENCE AFTER HOW MANY YEARS
DN-   DN—-DATA NOT AVAILABLE
SY-   SY- SYNCHRONOUS
ME-   ME- METACHRONOUS

SITE

The distribution of the MCGCT is similar to the solitary GCT, with the knee being the most common site (*2, 3, 6, 13, 22, 41, 50, 52, 61, 65, 67, 69*) with a few exceptions. Most of the MCGCT tumours in our review arose in the long bones of the lower extremity, predominantly around the knee ; this was followed in incidence by the proximal humerus and the distal radius as the next most common sites for occurrence of one of the lesions in the multicentric pathology. Many authors have reported an increased incidence of MCGCT in cases with tumours seen in the short bones of hands ; the incidence of multicentricity reportedly is almost double (at 3.9%) (*2, 11, 16, 28, 52, 61, 65*) as compared with the solitary GCT (< 2%) in bones of the hand and feet (*2, 9, 16, 17, 42, 43, 73*). The reviewed literature also reveals that MCGCT occurs more frequently in metaphyseal or meta-diaphyseal location (*19, 63*). Out of the 69 cases reviewed (190 lesions) in which the data regarding the loca-

tion of the lesions was available, 19 (10%) lesions were found to be located in the meta-diaphyseal region. Sim *et al* (*61*) reported 5 of 35 lesions (14%) to be located in the metaphysis. In comparison, tumours limited to the metaphysis or the meta-diaphysis account for less than 5% of all solitary GCT's (*9, 16*). From this review, a metaphyseo-diaphyseal situation was more common in reports of MCGCT ; Hoch *et al* (*28*), who have reported the largest series of MCGCT, reported 12 of 30 cases to be localised in this region, making this a finding of note. They also reported that the age range for their cases limited to the metaphysis was 12-15 years, and all but one were females.

INCIDENCE IN THE IMMATURE SKELETON

Solitary GCT is rare in the immature skeleton ; the incidence as reported by various authors averages less than 5% (*23, 43, 53, 58, 63*). Picci *et al* (*53*) in their series of 326 solitary GCTs found that only

Table III. — Large series of Giant Cell Tumours with reported multicentric cases

Author / Year	No of cases	Number of Multicentric cases
Williams *et al* (23), 1954, Mayo Clinic	101	02
Thomson *et al* (23), 1955	34	Nil
Murphy and Ackerman (23), 1956	31	DATA NOT AVAILABLE (DN)
Jaffe *et al* (23), 1958	60	1 (4 sites) DATA NOT AVAILABLE
Coley (23), 1958	DN	1 (2 sites) DATA NOT AVAILABLE
Hutter *et al* (23), 1962	76	DN
Mnaymneh *et al* (23), 1964, Massachusetts General Hospital	41	Nil
Wearne (74), 1968	39	Data not available
Goldenberg *et al* (23), 1970	218	4 CASES 21 y- Male-2 lesions 19 y- Male-2 lesions 21 y- Male-2 lesions 28 y- Female- 2 lesions
McGrath *et al* (44), 1972	52	1 CASE 4 lesions
Larsson *et al* (38), 1975	53	Nil
McIneervy and Middlemiss (43), 1978	138	1 CASE 24 y- Female-4 lesions 1 recurrence
Huvos *et al* (29), 1979	265	Nil
Sanerkin *et al* (59), 1980	86	4 CASES 2 of them were associated with Pagets disease
Schajowicz *et al* (60), 1981	362	Nil
Sung *et al* (64), 1982	218	Nil
EMSOS REVISION UNPUBLISHED DATA, 1989	677	3 CASES 32 y-Male-4 lesions 34 y-Female-2 lesions 31 y-Female-2 lesions
Dahlin and Unni (14),1986 Data on 8542 bone tumours	DN	4 CASES
McDonald *et al* (41), 1986	221	Nil (reported by Sim)
Campanacci *et al* (9), 1987	327	Nil
O Keefe *et al* (37), 1995	308	Nil
Biscaglia *et al* (6), 2000	29	Nil

1.8% were in the skeletally immature. All 218 patients reported by Goldenberg *et al* (23) were skeletally mature. This was not found to be true for MCGCT, as our review noted that 18 (21%) out of 83 MCGCT cases, where data for age was available, were seen in the skeletally immature. Hoch *et al* (28) reported 17 of 30 MCGCT cases (59%) being less than 20 years of age, with 13 being less than 16 years at presentation.

This may be a significant finding, and to the best of our knowledge, is a fact that has not been significantly highlighted.

LESIONS PER CASE

Multicentricity in GCT is defined when more than one lesion is encountered in a case. Most times 2 lesions are seen at presentation, or a separate lesion develops in a site where local spread cannot occur. The number of lesions in MCGCT has varied in the previous reports, with a total of 314 lesions reported in 83 cases. Out of these, 37 cases had 2 lesions, 19 had 3 lesions, 8 had 4 lesions, 7 had 5 lesions and the remaining had more than 5 lesions. Park *et al* (*50*) recorded the highest number of lesions (12 lesions) in a patient over many years. In the largest single series reported at one institute by Hoch *et al* (*28*), it was noted that MCGCT patients generally have 2 or 3 lesions. We could find no correlation between the number of lesions recorded and age or sex of the patient, nor the site of primary involvement, or the aggressiveness of the pathology.

Radiological features

The radiological features of GCT of bone are usually relatively distinctive ; most of the patients have typical radiolucent, eccentric, expansile lesions at the ends of the long bones. Radiologically MCGCTs are indistinguishable from the solitary GCT (*13, 16, 19, 27, 30, 42, 49, 52, 61, 63*) as far as the appearance of the individual lesions is considered. But the MCGCT site may be slightly different in the long bones, occurring more frequently at the metaphyseal and meta-diaphyseal region. Hoch *et al* (*28*) in a detailed clinicopathological evaluation noted a small minority of tumours with evidence of sclerosis and mineralisation, which are unusual radiographic features for a conventional GCT ; in multicentric situations this may suggest a fibro-osseous or bone forming tumour, but that point has not been proven. The histologic correlation to the sclerosis was abundant reactive bone that was prominent in fibro-histiolytic and aneurysmal bone cyst like areas. The present state of our knowledge reveals that there are no distinctive radiographic features that differentiate a solitary GCT from a MCGCT.

Histological features

In general, the literature reveals that MCGCT is histologically indistinguishable from solitary GCT (*13, 16, 19, 27, 28, 42, 52, 61, 63*). More importantly, the histologic appearances are of no significant value in predicting the behaviour of the lesion (*61, 70*). Some findings of different authors are worth mentioning ; Peimer *et al* (*52*) in their series of 5 cases noted that that the stroma in MCGCT tended to have many more spindle cells than in the typical solitary GCT. They also found areas of benign fibroblastic tumours in some cases, the explanation for which was not clear. These probably represent focal areas of scarring within the lesions and they are also found in other lesions such as aneurysmal bone cyst and fibrous dysplasia (*70*). Hoch *et al* (*28*) in their review also found that some of their cases contained fibroblastic and fibro-histiocytic areas surrounding the areas of classic giant cell tumour. They were of the opinion that the fibro-histiocytic areas are an accepted component of solitary GCT also, where these are seen in varying amounts.

Aggressiveness

The overall opinion of the reviewed literature seems to be that the individual lesions in a case of MCGCT are not more aggressive than their solitary counterparts and they respond to the conventional treatment in a manner similar to the lesions of unifocal giant cell tumour (*13, 28, 52, 71*). Of the 5 patients with 18 lesions reported by Peimer *et al* (*52*) recurrence occurred in 9 lesions (50%). Of the 8 lesions treated with or without autogenous bone grafting, six recurred. All lesions in the hand (3 lesions) which were treated with curettage alone recurred. Out of the 11 cases with 35 lesions reported by Sim *et al* (*61*), 6 lesions (17%) recurred. Hoch *et al* (*28*) in their review of 30 cases found a recurrence rate of 26% which is similar to the rate of recurrence reported in the solitary tumours (*9, 42*). There are some reports that MCGCT lesions appear to be more locally aggressive than their solitary counterparts and have higher rates of recurrence (*63*). Overall in our review we found 42 recurrences in 157 lesions (26%) in 65 cases (the data

was not available in remaining cases). We noted, as did Hoch *et al* (28), that the single most important factor related to the risk of recurrence was the incompleteness of surgical removal as the recurrence was highest (37%) in the lesions which were initially treated with curettage alone. The rate of recurrence was low in those where adjuvant therapy was used and where wide excision was done.

One case of osteosarcoma and one case of intermediate grade fibrosarcoma arising from previously diagnosed giant cell tumours has been documented in the literature reviewed by us, and this seems to be similar to malignancy rates reported for solitary GCTs (15).

TIME INTERVAL BETWEEN DIAGNOSIS OF LESIONS (SYNCHRONOUS VS METACHRONOUS LESIONS)

The tumours of MCGCT may be synchronous (lesions which are remote from one another but discovered within a short period of time and at similar stages of development) or metachronous (lesions which occur at different times and in different locations). Metachronous tumours have been thought to be metastatic or may represent a second, independent focus of disease (27).

Synchronous tumours occurring simultaneously at non-contiguous sites represent independent foci and have been labelled by some as benign metastasis (13, 27, 70). Subsequent contiguous foci may represent skip lesions, local recurrence or iatrogenic seeding that can manifest any time within a few years after initial surgery. Iatrogenic seeding occurs due to contamination of graft harvest site following curettage of giant cell tumour in the same sitting (16, 23, 61) but does not indicate multicentricity.

The incidence of synchronous tumours is reportedly more than the metachronous tumours, but the exact time interval beyond which to call it metachronous is not defined, and rough arbitrary time periods have been taken in different reports (13, 26, 51). Hoch *et al* (28) in 2006 classified tumours as being synchronous when multiple tumours had been discovered at the initial presentation or when a second tumour had been diag-

nosed within 6 months after the first. If the second tumour developed more than 6 months after the first lesion, the lesions were considered to be metachronous. Most of the non-contiguous tumours occurring within the first few years have been believed to be benign metastasis to the bone (5, 9, 13, 56, 61). When MCGCT affects contiguous bones or involves both sides of the joint space, direct tumour extension must be considered (27). This may be the case in the knee, as the highest incidence of multicentricity is reported here. There is a case reported by Hoch *et al* (28) where 3 lesions were seen at different parts of a single ulna over a 12-year period ; no adequate explanation could be given for this.

When we reviewed the literature, data regarding metachronous or synchronous origin was available for 66 cases, of which 29 were metachronous in origin (the time period between the index case and subsequent lesions being more than 1 to 1.5 years) and 37 were synchronous in origin. Haskell *et al* (26) in their review of literature opined that most of the MCGCTs are synchronous ; these occur within a poorly defined time of the initial tumour presentation. Since the difference between the definitions of these two terms is not very clear it is difficult to ascertain the exact incidence of metachronous and synchronous lesions. However Haskell *et al* (26) noted that a significant number of the subsequent lesions occurred within 3-4 years after the index lesion, the longest interval being 24 years. Our literature review corroborated these findings.

PATHOGENESIS OF MCGCT

The pathogenesis of multicentricity in GCT is still a topic for debate, with no consensus emerging after our literature review. Various mechanisms have been described, ranging from contiguous spread, iatrogenic seeding of tumour cells, benign metastasis, malignant transformation and *de novo* formation (13, 52, 61). Iatrogenic seeding usually manifests within a few years following the initial tumour surgery (13, 16, 23, 27, 51, 52, 61). It typically involves the graft donor site but skip sites within the same or adjacent bone have been reported in the pelvis (16). Direct tumour extension across the joint

following intra-articular breach (via synovial seeding) is a described mechanism (*22, 27, 39, 61*). Invasion of adjacent bone and soft tissue can also give rise to multifocal lesions, especially in the hand (*2, 23, 56*). Multiple foci occurring within short periods proximally along a limb may be due to lymphatic spread (*2, 39, 51, 52, 61, 74*). Most benign metastases usually occur within the first few years of diagnosis of the primary tumour ; however local invasion, and skip metastasis from the index case can occur more than 10 years after the primary is discovered (*13, 27, 51, 52, 56, 69*).

Hoch *et al* (*28*) postulated that the clinical and radiographic similarities between solitary GCT and MCGCT suggest that the lesions in MCGCT arise independently, rather being multiple sites of metastases from a single tumour, as no destructive pattern of metastatic disease was seen at any site. The characteristics may be similar to other polyostotic bone diseases where separate lesions exhibit radiological features of the solitary form. Additionally the biological behaviour of each lesion is usually independent of other lesions, as the outcome at each site is determined by the local management. It has also been postulated that the tendency of MCGCT to occur at younger patient ages may suggest a germ-line genetic abnormality that predisposes them to develop multiple tumours (*4, 7*), but we could not find any case where familial forms of MCGCT has been reported in the literature. This line of thought is something that needs to be explored in the future.

METASTASIS

Benign metastasis occurs in solitary GCT with an incidence of 1% to 6% (*5, 16, 34, 48, 56, 64*). The lungs are the most common site of benign metastasis but other affected sites include axial skeleton, appendicular skeleton, viscera, lymph node, brain, soft tissue (*13, 26, 48, 51, 56, 61, 62*). Two different sites of metastasis may be present concomitantly, especially occurrence of lymph node or bone with pulmonary metastasis in a case of benign giant cell tumour (*36, 55*).

Out of 69 cases reviewed with data sufficient to comment about metastatic disease, four cases of lung metastasis (5%) were documented (*15, 27*). Kay *et al* (*36*) reported 6 cases of pulmonary metastasis in 66 patients of solitary GCT (9%). From our review, we noted that patients with MCGCT do not seem to be at increased risk for pulmonary metastasis (*13, 28*). Most metastases are diagnosed within the first two years of diagnosis of the primary tumour, although they may be found as late as ten years or more afterwards (*5, 16, 33, 35, 36, 40, 44, 55, 56*). Most non-contiguous synchronous tumours occurring within the first few years have been postulated previously to be benign metastases to the bone (*9, 13, 56, 61*) but this has never been proven. The histology of benign metastasis is no different from the primary tumour (*5, 16, 23, 55, 56, 64, 76*). Malignant transformation in GCT following radiation treatment can also give rise to metastasis, but this is an extremely rare occurrence (*9, 23, 26*).

PATHOLOGICAL FRACTURE

Some authors have documented an increased incidence of pathological fractures in MCGCT (*6*). In our literature review the data regarding pathological fractures at presentation was available in 48 cases (128 lesions) of which 14 patients (15 lesions) were documented to have pathological fractures at presentation. This may be a feature of the delayed diagnosis, and may be related to the fact that many of these cases were in weight bearing areas ; it may have no bearing on the nature or aggressiveness of the disease process.

DIFFERENTIAL DIAGNOSIS

Various neoplastic and non-neoplastic conditions can present themselves as MCGCT, with the brown tumour of hyperparathyroidism probably being the most common one (*68*). This can be differentiated on clinical, radiological and histological grounds (*21, 27, 31, 32, 61*). Other neoplastic conditions involving multiple sites which may imitate MCGCT are osteochondroma, enchondroma, multiple myeloma, metastases, adamantinoma, angiosarcoma, fibrous dysplasia, fibrosarcoma, osteosarcoma, multifocal infection (*13, 16, 21, 27, 31, 32, 48, 68*). MCGCT can occur in association with Paget's disease and pheochromocytoma (*12, 54, 68*).

RECOMMENDATIONS

Since MCGCT occurs in less than 1% of GCT, regular screening of GCT patients for multi-centricity may not be cost effective (*13, 70*). Half yearly screening by either bone scan or skeletal survey (the former is to be preferred) is recommended for those patients with GCT at unusual sites (hands, meta-diaphyseal area), in females less than 20 years of age, and those diagnosed with multicentric initial involvement, to pick up late lesions. This is essential in the early diagnosis of any further lesions, and initiation of early treatment, which is reportedly the most significant factor influencing ultimate outcome. Our literature review showed that this protocol should be followed 6-monthly for at least 5 years, as most cases develop multi-centricity and additional lesions within this period. Monitoring can be done less frequently subsequently. Clinical monitoring and patient education is equally important in patients with MCGCT and will assist radiological screening. Although there are no specific parameters to identify which patient with GCT will develop multicentric lesions, our literature review suggests that GCT with primary lesions in the meta-diaphyseal region, GCT in an atypical location and in female patients in the younger age group (*13, 19, 53*) are to be followed carefully. Patients with multicentric giant cell tumour do not seem to be at increased risk of pulmonary metastasis and they respond to the conventional treatment in a similar manner to the unifocal tumours (*13, 63*).

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