Synovial chondrosarcoma

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Background: Synovial chondrosarcoma (SCH) is a very rare tumor arising in the intra-articular cavity. In the majority of literature reports it is described as a malignant transformation of a pre-existing synovial chondromatosis (SC). We reported a systematic review of primary and secondary SCH described in the literature with the aim to recollect data from different case-reports and case-series, trying to summarize general aspects of this very rare disease.

Methods: We collected 42 abstracts in the form of case series and case reports, which reported 67 cases of SCH. Studies were taken into account only if they proved a histological diagnosis of SCH, either primary or secondary, with or without evidence of pre-existing SC.

Results: The average age of SCH was 56.9 years, with prevalence for male sex. The average time of malignant transformation was 11.2 years. The most affected joint was the knee (47.7%), followed by hip (34.3%) and ankle (5.9%). SCH was described as de novo sarcoma only in 13 cases (19%). Surgery ended up with amputation in 59.7% of cases. Local recurrence rate was 28.3%.

Conclusions: We concluded that prognosis of SCH is worse than conventional one and we speculated this is due to the difficult site of the tumor (intraarticular), diagnostic delay and inappropriate previous treatments. We consider that a rapid deterioration of a SC or rapid recurrence after synoviectomy should be considered suspicious of malignant transformation and should be treated in a reference center.

Keywords: Synovial chondrosarcoma (SCH); malignant transformation; synovial chondromatosis (SC); synovial tumor

Introduction

Synovial chondrosarcoma (SCH) is a very rare type of chondrosarcoma (CHS) arising in the intraarticular cavity. The median age of patients is 50 years, with a slight prevalence in males (1). The most frequently affected joint is the knee, followed by hip, ankle, shoulder, elbow and wrist. SCH can be either primary or secondary to a pre-existing synovial chondromatosis (SC). In the majority of literature reports it is described as a malignant transformation of a pre-existing SC, but sporadically the occurrence of primary SCH has been observed (2,3).

The recommended treatment for SCH is extra-articular resection with wide surgical margins or amputation when limb salvage is not feasible due to tumoral involvement of the neurovascular bundle (1).

Synoviectomy, with or without joint replacement, has been described to be successful in low-grade tumors (4). According to Campanacci *et al.* the prognosis of SCH is comparable to that of conventional CHS and depends on the histological grade of malignancy of the lesion (1). It seems important to perform an adequate surgical treatment with wide margins, in order to avoid local recurrences, which appeared to be a bad prognostic factor (2).

We reported a systematic review of primary and secondary SCH described in the literature with the aim to recollect data from different case-reports and case-series, trying to summarize general aspects of this very rare disease, giving to pathologist, orthopedic surgeon and radiologist useful information. We analyzed general data, clinical

aspects, treatment, histology and follow-up, focusing on the diagnostic aspects, which remain a dilemma for orthopedic surgeon, radiologist and pathologist. In fact, to date, despite of Bertoni's criteria (2) have an important diagnostic role, no reliable clinical and imaging signs of malignant transformation of SC into SCH are indicated (4).

Methods

We performed a wide search in PubMed prior to December 2015, using the key words "synovial chondrosarcoma", "synovial tumors" and "synovial malignant transformation". We also screened the references of the searched articles for additional information. The language of the included articles was restricted to English and French. We collected 42 abstracts in the form of case series and case reports, which reported 67 cases of primary or secondary SCH. Full texts of the articles were collected from different electronic and paper archives. Studies were taken into account only if they proved a histological diagnosis of SCH, either primary or secondary, with or without evidence of pre-existing SC. Patients' information including age, sex, location of the tumor, duration of symptoms, treatments for SC, histological grade of CHS (when specified), treatments for SCH, local recurrence, metastasis and eventual outcome were all extracted from resources and summarized in *Table 1*. As the articles were reported from various clinical departments (e.g., Orthopedics, Radiology, Pathology), different aspects of the disease were reviewed focusing on the diagnostic aspects, which remain a dilemma for orthopedic surgeon, radiologist and pathologist.

Results

The average age of SCH diagnosis was 56.9 years, with prevalence for male sex (37 males and 23 females, with odds/ratio male female of 1.6). In 7 cases gender was not reported. The average time to develop SCH from SC was 11.2 years. The most affected joint was the knee (47.7%), followed by hip (34.3%), ankle (5.9%), shoulder (2.9%), elbow (2.9%), temporo-mandibular joint (2.9%), wrist (1.4%) and thumb (1.4%). SCH was described as de novo sarcoma only in 13 cases (19%) and consequently was secondary to SC in the rest of 45 cases (67.1%). In 9 cases etiology could not be proven due to the lack of information of the papers.

We divided treatments in two categories: treatments for SC and for SCH. Thirty-eight patients received

synoviectomies for SC, including arthroscopic synoviectomy. More than one synoviectomy was performed in 18 cases. Only 18 patients underwent biopsies (incisional or needle biopsy) as first treatment. Five patients underwent intralesional excision as first treatment. Three cases were first approached with marginal excisions. Fourteen patients underwent total joint replacement (usually associated with total or subtotal synoviectomy) of which 9 were total hip replacement (THR), 3 were total knee replacement (TKR) and 2 were total elbow replacement.

When histological diagnosis was specified, grade 2 CHS was the most frequent histotype (22 cases), followed by grade 1 CHS (7 cases) and grade 3 CHS (7 cases). The other cases were reported as CHS without histological grading.

Regarding treatment for SCH, only 14 patients underwent limb-salvage surgery. Amputations were performed in 40 patients (59.7%). Five patients refused hemipelvectomy and in 5 cases treatment was not reported. Two patients were treated with debulking surgery and one case was followed over time after marginal excision. Nineteen patients had local recurrence (28.3%). In 14 patients local status after treatment for SCH was not available. Nineteen patients developed metastases (28.3%), all localized to the lungs except in one case in which metastasis were localized to the scalp. Although adjuvant therapies are not indicated in CHS, we reported 6 cases of palliative radiotherapy, 4 cases of chemotherapy for metastatic disease and 2 cases of multimodal therapies for metastatic disease. At last follow-up, 34 patients had no evidence of disease (NED), 14 were dead of disease (DOD), 4 were alive with disease (AWD), and 6 were lost. In 9 cases outcomes were not reported. When there was a match between histological grade of malignancy and outcome, we reported that among grade 3 SCH, 3 patients were DOD, 1 was AWD and only 3 patients had NED. Among grade 2 CHS, 6 patients were DOD, 14 had NED and 1 was AWD. Among grade 1 CHS, 3 patients had NED, 1 was DOD and 1 was lost. When there was a match between site of disease and outcome, survivals were similar. In fact, when the disease was localized to the knee, 15 patients (46.8%) had NED and 6 (18.7%) were DOD. When the disease was localized to the hip, 11 patients (47.8%) had NED and 7 (30%) were DOD.

Conclusions

SC is a rare benign disorder originating from the synovium, as result of self-limiting proliferative and metaplastic

Table 1 General data, clinical aspects, treatments and outcomes of the 67 cases reported

Author	Age at diagnosis of SC (years)	Sex	Site	Treatment(s) for SC	Time to malignancy (years)	Histotype	Treatment(s) for CHS	Local recurrence	Metastasis	Outcome	Type
Nixon (5), Brannon and Tracey (6)	34	M	Hip	Syn	0	CHS	Debulking-HA	No	Lung	DOD	De novo
Castleman et al. (7)	72	M	Knee	IB	0	Low grade CHS	Amp	N/A	N/A	Lost	De novo
Goldman et al. (8)	58	M	Knee	IB-2 syn	0	CHS	Mid-thigh amp	Lost	N/A	Lost	De novo
	41	M	Knee	IB-syn	0	CHS	Amp	Lost	N/A	Lost	De novo
	37	M	Knee	Marginal excision	0	CHS	None	No	N/A	NED	De novo
Mullins et al. (9)	29	F	Knee	2 syn	14	High grade CHS	Hip disarticulation	No	Lung	AWD	Secondary
King et al. (10)	38	M	Knee	Syn	5	CHS	RXT-debulking-AKA	No	No	NED	Secondary
Dunn et al. (11)	42	M	Knee	Needle biopsy	25	CHS	Hip disarticulation	No	Scalp	AWD	Secondary
Kaiser et al. (12)	38	F	Ankle	3 IE	9	CHS	BKA	No	No	NED	Secondary
Wu et al. (13)	34	M	Knee	IE-IB	1	CHS	AKA	No	No	NED	Secondary
Kindblom and Angervall (14)	37	M	Ankle	IB	0	Myxoid CHS	Lower-leg amp	No	No	N/A	De novo
Hamilton et al. (15)	58	M	Knee	Syn	N/A	CHS	AKA	Yes	Lung	N/A	Secondary
Hamilton et al. (16)	25	M	Knee	3 syn-marginal excision	25	High grade CHS	Hip disarticulation	No	No	NED	Secondary
Perry et al. (17)	27	F	Knee	2 syn-IE	24	Grade 2 CHS	AKA-hemip-pulmonary lobectomy-RXT-CHT	Yes	Lung-brain	DOD	Secondary
Manivel et al. (18)	35	M	Knee	IB	15	Low grade CHS	Debulking-2 wide resections	Yes	No	N/A	Secondary
Benoit et al. (19)	58	F	Knee	Arthroscopy-2 syn	0	Grade 2 CHS	AKA	No	No	NED	De novo

Table 1 (*continued*)

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Author	Age at diagnosis of SC (years)	Sex	Site	Treatment(s) for SC	Time to malignancy (years)	Histotype	Treatment(s) for CHS	Local recurrence	Metastasis	Outcome	Type
Bertoni et al. (2)	44	F	Hip	Syn	3	Grade 2 CHS	THR + intralesional excision-hemip	Yes	No	NED	Secondary
	50	M	Knee	IE-syn	2	Grade 2 CHS	Midthigh amp-CHT-HA	Yes	Lung-limph node	DOD	De novo
	57	F	Elbow	Total elbow replacement	N/A	Grade 3 CHS	Shoulder disarticulation-3 metastasectomies-CHT	Yes	Lung	DOD	Secondary
	37	F	Ankle	IE-2 syn	10	Grade 1 CHS	BKA	Yes	No	NED	Secondary
	63	F	Knee	2 IE	1	Grade 2 CHS	Intralesional excision-AKA	Yes	Lung-sternum	DOD	Secondary
	66	F	Hip	THR	N/A	Grade 1 CHS	N/A	Lost	N/A	Lost	Secondary
	25	M	Knee	Syn-IE	5	Grade 2 CHS	Midthigh amp-metastasectomy	Yes	Lung	NED	Secondary
	27	F	Knee	2 syn	24	Grade 2 CHS	AKA-CHT-RXT-hemip-metastasectomy	Yes	Lung-brain	DOD	Secondary
	70	M	Hip	THR	0	Grade 2 CHS	Hemip	No	No	NED	De novo
	40	M	Knee	2 syn	3	Grade 2 CHS	Knee arthrodesis + intralesional excision	No	No	NED	Secondary
Kenan et al. (20)	74	M	Knee	Arthroscopy	N/A	CHS	Arthrotomy + syn	Yes	No	NED	Secondary
Ontell et al. (21)	64	M	Ankle	Marginal excision	0	Grade 2 CHS	BKA	No	No	NED	De novo
Anract et al. (22)	36	M	Hip	IB	N/A	Grade 2 CHS	WR + THR	No	No	NED	Secondary
	62	M	Knee	IB	N/A	Grade 2 CHS	AKA	No	No	NED	Secondary
	40	F	Shoulder	IB	N/A	Grade 2 CHS	WR and shoulder replacement	No	No	NED	Secondary
	51	F	Knee	4 Syn	25	Grade 2 CHS	AKA-disarticulation	Yes	No	NED	Secondary
	58	F	Knee	Syn-IB	1	Grade 2 CHS	AKA	No	No	NED	Secondary
	44	M	Knee	3 Syn-IB	3	Grade 2 CHS	AKA	No	No	NED	Secondary
Bascoulerge et al. (23)	40	M	Knee	Syn	N/A	CHS	WR	Yes	No	N/A	N/A

Table 1 (*continued*)

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Author	Age at diagnosis of SC (years)	Sex	Site	Treatment(s) for SC	Time to malignancy (years)	Histotype	Treatment(s) for CHS	Local recurrence	Metastasis	Outcome	Type
Hermann et al. (24)	55	M	Hip	THR	N/A	CHS	N/A	Yes	Lung	DOD	N/A
Wuisman et al. (25)	50	F	Hip	Syn	N/A	CHS	WR + endoprosthesis	No	No	NED	N/A
	30	M	Hip	Syn	N/A	CHS	WR + endoprosthesis	No	No	NED	N/A
Merrill et al. (26)	50	F	TMJ	Marginal excision	3	CHS	None (she refused)	No	No	NED	Secondary
Taconis et al. (27)	55	M	Hip	Syn	4	CHS	N/A	No	No	DOD	N/A
Davis et al. (28)	25	M	Knee	N/A	N/A	CHS	AKA	N/A	N/A	Lost	N/A
	58	M	Knee	N/A	N/A	CHS	AKA	Yes	Lung	DOD	N/A
Blokx et al. (29)	64	M	Hip	3 syn-IB	10	Grade 1 CHS	None (he refused hemip)	N/A	No	DOD	Secondary
Hallam et al. (4)	45	M	Knee	Syn	N/A	CHS	TKR	No	No	NED	N/A
Wenger et al. (3)	69	M	Thumb	IB	0	CHS	WR	No	No	NED	De novo
Wittkop et al. (30)	N/A	N/A	Knee	Syn-TKR	N/A	Low grade CHS	N/A	N/A	N/A	N/A	Secondary
	N/A	N/A	Hip	2 IB	N/A	Dedifferentiated CHS	N/A	N/A	Lung	DOD	Secondary
Sperling et al. (31)	55	F	Hip	2 syn-THR	8	Low grade CHS	Hemip-2 marginal excisions	Yes	N/A	AWD	Secondary
	31	F	Hip	Several biopsies	11	CHS	None (she refused hemip)	No	Lung	Lost	Secondary
Bhadra et al. (32)	81	M	Knee	Needle biopsy-syn	1	CHS	AKA	No	No	NED	Secondary
Sah et al. (33)	47	M	Shoulder	Syn-hemiarthroplasty	N/A	CHS	Scapulectomy+forequarter amp	Yes	Lung	N/A	N/A
Campanacci et al. (1)	31	M	Hip	IB	23	Grade 2 CHS	Hemip	No	No	NED	Secondary
	60	F	Hip	2 IB	10	Grade 2 CHS	RXT (she refused hemip)	No	No	AWD	Secondary
Zamora et al. (34)	47	F	Hip	IB	15	Grade 2 CHS	Frozen biopsy-hemip-metastasectomy	No	Lung	N/A	Secondary
	60	M	Hip	2 syn-THR-2 IB	3	Grade 3 CHS	Hemip	No	No	NED	Secondary
Schlachter et al. (35)	34	F	Hip	IB	3.5	CHS	Hemip	No	No	NED	Secondary

Table 1 (*continued*)

Table 1 (continued)

Author	Age at diagnosis of SC (years)	Sex	Site	Treatment(s) for SC	Time to malignancy (years)	Histotype	Treatment(s) for CHS	Local recurrence	Metastasis	Outcome	Type
Rybak et al. (36)	45	M	Hip	Syn-THR	0	Grade 2 CHS	WR	Yes	No	NED	De novo
Muramatsu et al. (37)	64	M	Elbow	Elbow replacement-curettage	2	Grade 3 CHS	RXT (he refused amputation)	Yes	No	NED	Secondary
Yao et al. (38)	46	F	Knee	Syn-TKR	5	Grade 1 CHS	None	No	No	N/A	Secondary
Kyriazoglou et al. (39)	44	M	Wrist	Biopsy	10	Grade 1 CHS	WR + external fixation	N/A	N/A	N/A	Secondary
Coleman et al. (40)	63	F	TMJ	Needle biopsy	0	CHS	WR + RXT	No	No	NED	Secondary
Evans et al. (41)	23	N/A	Hip	3 syn	2.7	Grade 1 CHS	HA	N/A	No	NED	Secondary
	48	N/A	Hip	THR	11.3	Dedifferentiated CHS	Debulking	N/A	Lung	DOD	Secondary
	25	N/A	Hip	2 arthroscopies-THR	20	Grade 2 CHS	Debulking	N/A	Lung	DOD	Secondary
	25	N/A	Hip	Multiple syn-THR	39	Grade 1 CHS	HA	N/A	No	NED	Secondary
	19	N/A	Knee	Multiple arthroscopies-TKR	38.5	Grade 2 CHS	AKA	N/A	Lung	DOD	Secondary
Jonckheere et al. (42)	45	F	Knee	Arthroscopy-syn	0	CHS	AKA	No	No	NED	De novo

SC, synovial chondromatosis; CHS, chondrosarcoma; M, male; F, female; TMJ, temporomandibular joint; Syn, synoviectomy; IB, incisional biopsy; IE, intralesional excision; N/A, not available; THR, total hip replacement; TKR, total knee replacement; AKA, above knee amputation; BKA, below knee amputation; RXT, radiotherapy; CHT, chemotherapy; Hemip, hemipelvectomy; HA, hindquarter amputation; Amp, amputation; WR, wide resection; DOD, dead of disease; NED, no evidence of disease; AWD, alive with disease.

changes in the synovial membrane of the joints, tendon sheaths, or bursae, leading to formation of intrasynovial cartilaginous nodules (43). The disease was first described by Leannac in 1813; however, its current description was not applied until 1958 by Jaffe (44). Two types of SC have been described (45): in primary SC the metaplasia takes place within the synovial membrane and the cartilage nodules later detach from the synovium forming loose bodies in the joint cavity; in secondary SC the cartilage nodules may develop in the presence of intra-articular cartilage loosened bodies. In primary SC the histological pattern is characterized by nodules with irregular cellularity and focal atypia of chondrocytes. The secondary form, characterized by reactive cartilaginous nodules and indolent course, is most related to degenerative joint disease, osteochondritis dissecans, rheumatoid arthritis and trauma (1).

The exact prevalence of SC is unknown but it usually affects the third to fifth decades of life (46), with men being affected two to four times more frequently than women (47). The knee is the most commonly affected large joint followed by hip, shoulder, elbow, ankle and wrist (24). Patient' clinical symptoms typically include pain, swelling and restricted joint movement (48). The symptoms are often insidious at disease onset and are gradually progressive, although rare spontaneous regression has been reported (49).

The most widely quoted classification for SC is by Milgram and combines radiographic and histopathological features to describe three types of disease: the first, type 1or early stage, where there are synovial-based masses without intra-articular loose bodies; the second, type 2 or intermediate stage, where there are synovial-based masses and free intra-articular loose bodies; and finally the third, type 3 or late stage, with multiple free osteochondral loose bodies without demonstrable synovial disease (50). In a recent case series of 20 SCs, the most frequent was type 1 (65%), followed by type 2 (25%) and type 3 (10%) (30).

Radiological findings of SC are variable depending upon the level of calcification of the cartilaginous nodules, but in most cases imaging is fairly diagnostic (43). Radiographs, computed tomography (CT) and magnetic resonance imaging (MRI) show evidence of an intra-articular soft tissue mass with multiple mineralized osteocartilaginous nodules constituting the lesion and well-defined bone erosions on both sides of the joint (51). In non-mineralized lesions the MRI displays an intra-articular conglomerate mass isointense relative to muscle on T1-weighted images and hyperintense on T2-weighted images. In lesions with calcified cartilaginous nodules small areas of low signal-

intensity are observed on a pulse sequence (52). From a histological point of view, SC demonstrates coalescent and well circumscribed hypercellular lobules of hyaline cartilage attached to the synovium. Typically, the cartilage cells are arranged in clustered patterns. In most cases the lesions show high hypercellularity and nuclear atypia. Myxoid change is rare and when present it is only focal; necrosis is absent (43,51). The treatment often involves removal of loose bodies and subtotal synoviectomy, with or without joint replacement. Local recurrence is possible after incomplete synoviectomy, inadequate removal of loose bodies or diseased synovium at the time of initial surgery (28,32,43) and it is estimated to be 23% (53).

Primary SC has a higher tendency to malignant transformation into SCH than secondary SC (2). This risk ranges from 1% to 5% according different case series (28,36,53). As the clinical and radiological features are very similar between SC and SCH, their differentiation is often difficult and represents a diagnostic problem for orthopedic surgeon, radiologist and pathologist. Because of the differences in treatment and prognosis between the two pathologies, attempts have been made to identify features that might aid in differentiating the two entities (36). However, many authors have found significant overlap with no definitive clinical or radiologic criteria of malignancy that can be used to distinguish SC from SCH (2,27,30,34,53). Clinically, both may present with pain, swelling and restricted movement of the affected joint with longstanding symptoms. Several authors speculate that a rapid deterioration of a longstanding clinical history or rapid recurrence after synoviectomy may indicate malignant transformation (31,34,53).

From a radiological point of view a permeated and destructive pattern rather than an erosive one is suspicious for malignancy (25). In contrast, Wittkop et al. did not observe any MRI features to distinguish the malignant changes of a SC (30).

Several authors have tried to identify reliable diagnostic criteria. In 1991, Bertoni et al. indicated the histopathological features to differentiate SC from SCH (2). In their opinion, the cartilage cells, arranged in clusters in SC, tended to arrange in sheets without clustering effect in SCH. In SCH there was an evident myxoid change in the matrix and hypercellularity with round and spindle cell appearance. In addition, areas of necrosis were seen in SCH, which were a sign of malignancy. At the interface between tumor and healthy bone, SC was seen to erode the bone with "pushing margins", while the SCH had a permeated behavior with

typical "filling-up" of marrow spaces. In 1996, Anract *et al.* (22) sustained that three conditions have to be respect to demonstrate the malignant transformation of a SC: a pre-existing SC proven histologically; actual CHS proven histologically; coexistence of both areas of SC and CHS in the resected specimen. They also indicated that the only MRI criterion of malignancy was the invasion of the bone medullar canal. More recently, in 2003, Sperling *et al.* (31) speculated that the under-expression of the BCL-2 (a cell survival marker) in SCH could be used as diagnostic immunohistochemical tool. Moreover, cytogenetic data can offer important information for the diagnosis and our understanding of the development of SCH from SC. In 2013, Kyriazoglou *et al.* (39) performed a cytogenetic analysis of a secondary SCH in a 54-year-old man, finding a novel chromosomal translocation between chromosome 1 and 14.

From our systematic literature review, we can assess that SCH is a very rare disease, with only 67 cases reported in the literature. We were able to document all cases. In the majority of them (67.1%) the disease was secondary to malignant transformation of a pre-existing SC, with an average time to malignancy of 11.2 years. No etiological factors can be indicated, even though in some cases there is a history of trauma. No familiar cases were reported. Surgery ended up with amputation in 59.7% of cases. Local recurrence rate was 28.3%. Taking into consideration that most of cases were grade 2 CHS, these data are not acceptable and not comparable to those of conventional CHS.

We concluded that prognosis of SCH is worse than conventional CHS and we speculated this is due to the difficult site of the tumor (intra-articular), diagnostic delay and subsequent inappropriate previous treatments. An important limit of this study is that some papers do not report complete information and some cases are reported as CHS without histological grade.

To date, no reliable clinical and imaging signs of malignant transformation of SC into SCH are indicated. We consider diagnosis difficult and often achieved with important delay. Average time to malignancy is 11.2 years and it can be considered not only as part of the natural history of the disease, even as diagnostic delay, because we do not exclude that the tumor could be a SCH from the onset. Diagnosis is possible only with the cooperation of orthopedic surgeon, radiologist and pathologist and can be achieved evaluating clinical aspects, radiological findings and histopathological features case by case. We consider that a rapid deterioration of a longstanding disease or rapid recurrence after synoviectomy should be considered

suspicious of malignancy and should be treated at, or referred to, a tertiary hospital familiar with managing these often complex tumors. Since most amputations were done for recurrence after inappropriate surgery, wide resection margins achieved at primary surgical procedure might improve the limb salvage rate in these patients.

Acknowledgements

Footnote

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