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Chapter 1

General introduction

General introduction

Enchondromas are common intra-osseous benign cartilaginous neoplasms that develop in close proximity of the growth plate cartilage.

Chondrosarcoma are malignant bone neoplasms, characterized by the production of cartilage instead of bone.

When multiple enchondromas are present, this condition is called enchondromatosis, also known as Ollier disease. The condition in which enchondromatosis is associated with soft tissue hemangiomas is known as Maffucci syndrome.

Nomenclature/ synonyms:

Enchondroma

Chondrosarcoma:

- Borderline chondrosarcoma/ low-grade chondrosarcoma/ grade I chondrosarcoma/ atypical cartilaginous tumour
- Chondrosarcoma grade II
- Chondrosarcoma grade III

Ollier disease: dyschondroplasia/ multiple cartilaginous enchondromatosis/ enchondromatosis Spranger type I/ multiple enchondromas/ dyschondroplasia

Maffucci syndrome: dyschondrodysplasia with hemangiomas/ enchondromatosis with multiple cavernous hemangiomas/ Kast syndrome/ hemangiomatosis chondrodystrophica/ enchondromatosis Spranger type II.

Atypical cartilaginous tumour/grade I central chondrosarcoma

Introduction

Within the group of chondrosarcomas, different subtypes are defined. In the context of this thesis, we focused on conventional central chondrosarcoma. These neoplasms may arise *de novo* in the medulla of the bone (primary) or in a pre-existent enchondroma (secondary).¹ Atypical cartilaginous tumour (ACT)/grade I central chondrosarcoma form approximately 85% of all conventional chondrosarcomas. Over the course of time the definitions of chondrosarcoma have been adapted based upon clinico-pathological and radiological correlations. Given the fact that a grade I chondrosarcoma in the extremities when bona-fide sampled will never metastasize unless dedifferentiation occurs and behaves like a locally aggressive lesion, the WHO committee introduced the concept of atypical cartilaginous tumour,² in analogy with lipomatous tumours.

The most important prognostic factors in predicting the risk for metastasis are grading of the tumour and age of onset above 50 years. Grading is based on cellularity, nuclear size, nuclear staining, hyperchromasia and mitoses.^{3,4} While grade I and II rarely metastasize (respectively 0% and 10%), grade III chondrosarcomas do so in about 70% of the cases. The 5-years survival in grade I chondrosarcoma is 84%, in grade II 64% and in grade III 29%. The main reason for the lower than expected 100% survival in ACT/ grade I central chondrosarcoma is the problem of local control in lesions of the skull, scapula or pelvis.^{5,6}

Diagnosis

The presence of persistent pain not related to mechanical problems lasting for a period of several weeks should raise attention. Swelling might not at all be the presenting symptom. Even more puzzling is that a substantial number of these tumours are found as an accompanying event by radiological examination for another reason. The diagnosis should be made in a multidisciplinary setting based on clinical, radiological and histological findings. Specific clinical practice guidelines for diagnosis are published by the ESMO working group⁷.

Treatment

Surgery is the treatment of choice for malignant cartilage neoplasms, with the extend of the margins depending on the tumour grade and location.^{6,7} Radiotherapy and chemotherapy have no substantial role in the treatment of chondrosarcomas.^{7,8}

Until the 90's, for all grades of central chondrosarcoma, wide resections and reconstruction (often with the use of a joint-replacing prosthesis), were performed. Due to the fact that morbidity had been high, but mortality low, less aggressive surgical methods were introduced in patients with low-grade central chondrosarcoma. Since 1994, the Leiden University Medical Center treated this patient group by intralesional curettage. After instillating the walls of the cavity with phenol 85%, ethanol 96% is used for washing out the phenol. Finally, the bone cavity is filled up with deep-frozen, non-irradiated allograft bone chips derived from donor femoral heads (Bio Implant Services, Leiden, The Netherlands).

Phenol

Liquefied phenol, containing 82 to 86.5% w/w phenol in water, is a colourless or faintly coloured liquid. It may be used as a preservative in pharmaceuticals and chemicals. Liquefied phenol causes cell-wall disruption, precipitation, denaturation of proteins and coagulation necrosis. Liquefied phenol is readily absorbed via inhalation, ingestion and dermal contact, causing both local and systemic toxicity. The elimination half-time ranges from 1-14 hours.¹² It is eliminated in the urine, mainly as sulfate and glucuronide conjugates. Clinical symptoms of phenol ingestion may include local corrosion with pain, nausea, vomiting and diarrhea. Systemic toxicity may consist of CNS depression, circulatory and respiratory failure, pulmonary edema and hepatic and renal injury. Applied tot the skin, phenol causes blanching and corrosion in a concentration of 1-2%, depending on the exposure time.¹³⁻¹⁶

Macroscopy

Chondrosarcoma displays a translucent, lobular, blue-grey or white surface due to the presence of hyaline cartilage. Yellow-white, chalky areas of calcium deposit are commonly present. There may be areas containing mucoid material and cystic changes. In higher grades, cortical destruction or extended growth into the soft tissue may occur.²

Histopathology

The distinction between enchondroma and ACT/ grade I central chondrosarcoma can be difficult, and is subjected to a higher inter-observer variability.³ In ACT/ grade I central chondrosarcoma, the chondrocytes are atypical, varying in size and shape and contain enlarged, hyperchromatic nuclei. Binucleation is frequently seen, but mitosis is absent.⁴

Follow-up

In the postoperative period up to three months, plain radiographs are performed to detect bone repair of the bone window, or any complications like fractures. From 6-12 months after surgery, dynamic MR images with the use of Gadolinium are accomplished periodically to detect any residual or recurrent cartilage tumour.

Ollier disease and Maffucci syndrome

Introduction

While most enchondromas and/or conventional chondrosarcoma are solitary, some occur multiple in the context of a syndrome; enchondromatosis. The two best-known are Ollier disease and Maffucci syndrome.¹⁷⁻¹⁹ Both are characterized by the presence of multiple enchondromas. The difference is that in Maf-

fucci syndrome, also benign vascular lesions (hemangiomas) and/or lymphangioma are present. Both syndromes are non-hereditary. Often one site of the body is affected. The unilateral distribution of enchondromas could point in the direction of an early mutation event in embryogenesis, resulting in mosaicism.

Diagnosis

Diagnosis is based on clinical features and plain radiographs of the bone. Usually, these syndromes manifest in early childhood; 75% are diagnosed before the age of twenty years.²⁰

Besides the short and long tubular bones, also flat bones of the scapula and pelvis can be affected. Due to the asymmetrical distribution of enchondroma, often bowing deformities and/or limb length deformities occur.^{20,21}

Treatment

There is no medical treatment for enchondromatosis. Surgery is indicated in case of complications, such as growth defects, pathological or pending fractures or malignant transformation.

Microscopy

Histological grading in enchondromatosis is more difficult, as increased cellularity and some nuclear atypia are not sufficient to diagnose low-grade chondrosarcoma. The distinction between benignity and malignity should be made within a multidisciplinary team. Also, radiological features should be taken into consideration (e.g. cortical destruction, soft tissue extension).

Genetics

Both Ollier disease and Maffucci syndrome are non-hereditary. Mutations in the gene encoding for isocitrate dehydrogenase 1 (IDH1) and IDH2 were detected

in solitary cartilaginous tumours as well in patients with enchondromatosis. These mutations might represent early postzygotic genetic events and account for the initiation of the disease process. Mutations of the gene encoding for parathyroid hormone receptor 1 (PTH1R) are found in a small subset (~10%) of patients with Ollier disease.²²⁻²⁵

Malignant transformation

The risk to develop secondary chondrosarcoma is 40% in Ollier disease (range 5-50) and up to 53% in Maffucci syndrome.²⁰

Aim of the thesis

Regarding cartilage neoplasms of the bone, this thesis could be divided in two different parts;

The **first aim** was trying to identify clinical characteristics in a large group of patients suffering from Ollier disease or Maffucci syndrome in order to predict the risk of secondary development of chondrosarcoma and its subsequent mortality. The **second aim** was to prove the assumption that phenol indeed has an effective role as local adjuvant in patients suffering from central grade I chondrosarcoma/atypical cartilaginous tumour of the long bones.

Therefore we investigated two aspects;

First, the *in-vitro* cell-killing potential of phenol was studied. Secondly, phenol-concentrations during surgery were measured.

To prove the clinical effect on patients, we studied a group of patients treated with phenol as adjuvant therapy following intralesional curettage.

Also, the role of MRI imaging in the follow-up in these patients was studied.

Outline of the thesis:

In **chapter two**, an international multicenter study was performed to gain more insight in the clinical behaviour and characteristics of enchondromas in patients with Ollier disease and Maffucci syndrome. An important aim was to es-

estimate the cumulative probability of secondary transformation of enchondroma to chondrosarcoma over a lifetime. Variables who significantly were associated with the transformation to chondrosarcoma and mortality were defined.

In **chapter three**, the cytotoxic action of phenol on different cell lines were studied in order to provide a rationale for its use as an adjuvant. We investigated potentially effective concentrations *in vitro*.

Besides the expected cytotoxic effect of phenol on cell lines, we also analysed the independent effect of ethanol at different concentrations to assess cytotoxicity. In **chapter four**, the surgical technique was outlined in more detail regarding the use of phenol and ethanol as adjuvant therapy following intralesional curettage of the cartilage tumour. Firstly, the initial local concentration of phenol in the cavity wall was measured. Secondly, we investigated the dilution of phenol 85% by ethanol 96%, and the role of the size of the cavity in the degree and speed of dilution.

Chapter five describes the results of intralesional curettage, followed by phenol application as adjuvant therapy and bone grafting. Aim was to describe clinical outcomes in a retrospective study.

Chapter six concerns the follow-up of patients suffering from ACT/ grade I central chondrosarcoma and those that were treated by intralesional curettage as described above. Already studies were performed on the predictive values of (dynamic) Gd-MR imaging in the preoperative diagnosis and grading of the lesion. So far, no results were published on the postoperative follow-up in these groups of patients. The outline of the study was to identify MR imaging features of normal postoperative changes and local residual or recurrent disease. Next to this, we tried to identify characteristics by using postoperative MR images to design a flow chart for different follow-up and treatment options.

References

1. Huvos AG. Bone tumours. Diagnosis, treatment, and prognosis. 2 ed. Philadelphia: W.B. Saunders Company; 1991.
2. Fletcher CD, Bridge JA, Hogendoorn PC et al. WHO classification of Tumours of Soft Tissue and Bone. Fourth edition ed. Lyon IARC Press: 2013.
3. Eefting D, Schrage YM, Geirnaerd MJ et al. Assessment of interobserver variability and histologic parameters to improve reliability in classification and grading of central cartilaginous tumours. *Am J Surg Pathol* 2009 Jan;33(1):50-7.
4. Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. *Cancer* 1977 Aug;40(2):818-31.
5. Björnsson J, McLeod RA, Unni KK et al. Primary chondrosarcoma of long bones and limb girdles. *Cancer* 1998 Nov 15;83(10):2105-19.
6. Gelderblom H, Hogendoorn PC, Dijkstra SD et al. The clinical approach towards chondrosarcoma. *Oncologist* 2008 Mar;13(3):320-9.
7. Hogendoorn P. Bone sarcomas: ESMO Clinical Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2010;21(Supplement 5):v204-v213.
8. Bovée JV. Cartilage tumours and bone development: molecular pathology and possible therapeutic targets. 2010 Jul.
9. Eriksson AI, Schiller A, Mankin HJ. The management of chondrosarcoma of bone. *Clin Orthop Relat Res* 1980 Nov;(153):44-66.
10. Krochak R, Harwood AR, Cummings BJ et al. Results of radical radiation for chondrosarcoma of bone. *Radiother Oncol* 1983 Nov;1(2):109-15.
11. Lee FY, Mankin HJ, Fondren G et al. Chondrosarcoma of bone: an assessment of outcome. *J Bone Joint Surg Am* 1999 Mar;81(3):326-38.
12. Bentur Y, Shoshani O, Tabak A et al. Prolonged elimination half-life of phenol after dermal exposure. *J Toxicol Clin Toxicol* 1998;36(7):707-11.
13. Caravati EM. Household Products. In *Medical Toxicology*. [201]. Edited by: Dart RC. Lippincott: Williams and Wilkins; 2004:1294-1303, Ref Type: Edited Book.
14. Horch R, Spilker G, Stark GB. Phenol burns and intoxications. *Burns* 1994, 20:45-50.
15. Hunter DM, Timerding BL, Leonard RB et al. Effects of isopropyl alcohol, ethanol, and polyethylene glycol/industrial methylated spirits in the treatment of acute phenol burns. *Ann Emerg Med* 1992, 21:1303-1307.
16. Monteiro-Riviere NA, Inman AO, Jackson H et al. Efficacy of topical phenol decontamination strategies on severity of acute phenol chemical burns and dermal absorption: *in vitro* and *in vivo* studies in pig skin. *Toxicol Ind Health* 2001, 17:95-104.
17. Maffucci A. Di un caso encondroma ed angioma multiplo. *Movimento medico-chirurgico*, Napoli 1881;3:399-412; 565-575.
18. Ollier M. De la dyschondroplasia. *Bull Soc Chir Lyon* 1899;3:22-3.
19. Ollier M. Dyschondroplasia. *Lyon Med* 1900;93:23-5.
20. Verdegaal SH, Bovée JV, Pansuriya TC et al. Incidence, predictive factors, and prognosis of chondrosarcoma in patients with Ollier disease and Maffucci syndrome: an international multicenter study of 161 patients. *Oncologist* 2011;16(12):1771-9.
21. Fletcher CD, Bridge JA, Hogendoorn PC et al. WHO Classification of Tumours of Soft Tissue and Bone. IARC: Lyon; 2013.

22. Couvineau A, Wouters V, Bertrand G et al. PTHR1 mutations associated with Ollier disease result in receptor loss of function. *Hum Mol Genet* 2008 Sep 15;17(18):2766-75.
23. Hopyan S, Gokgoz N, Poon R et al. A mutant PTH/PTHrP type I receptor in enchondromatosis. *Nat Genet* 2002 Mar;30(3):306-10.
24. Pansuriya TC, Oosting J, Krenacs T et al. Genome-wide analysis of Ollier disease: Is it all in the genes? *Orphanet J.Rare.Dis.* 6,2. 2011.
25. Rozeman LB, Sangiorgi L, Bruijn IH et al. Enchondromatosis (Ollier disease, Maffucci syndrome) is not caused by the PTHR1 mutation p.R150C. *Hum Mutat* 2004;24(6):466-73.

