Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 253–257

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

The association of enchondromatosis with malignant transformed chondrosarcoma and ovarian juvenile granulosa cell tumor (Ollier disease)

Andrea Burgetova [a], Zdenek Matejovsky [b], Michal Zikan [c], Jiri Slama [c], Pavel Dundr [d], Petr Skapa [e], Kamila Benkova [f], David Cibula [c], Daniela Fischerova [c, *]

[a] Department of Radiology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic
[b] Orthopedic Clinic, Bulovka Hospital, First Faculty of Medicine, Charles University, Czech Republic
[c] Gynecologic Oncology Center, Department of Obstetrics and Gynecology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic
[d] Department of Pathology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic
[e] Department of Pathology, Second Faculty of Medicine, Charles University, Czech Republic
[f] Department of Pathology, Bulovka Hospital, First Faculty of Medicine, Charles University, Czech Republic

ARTICLE INFO

Article history:
Accepted 28 July 2016

Keywords:
chondrosarcoma
enchondromatosis
juvenile granulosa cell tumor
Ollier disease
ultrasound

ABSTRACT

Objective: Ovarian juvenile granulosa cell tumor has an interesting association with multiple enchondromatosis (Ollier disease and Maffucci syndrome) and should be considered a leading diagnosis when an ovarian mass is found in young patients with these conditions. Besides the association with nonskeletal malignancies, there is a high risk of malignant transformation of enchondroma in chondrosarcoma as was also the case in this instance.
Case Report: The report uses multiple images to document the representative and characteristic markers of multiple enchondromas in a 22-year-old patient with Ollier disease complicated by malignant transformation of chondrosarcoma and in whom the disease is associated with ovarian juvenile granulosa cell tumor of the right ovary.
Conclusion: It is important to recognize that when the female patient presents with enchondromatosis and a large unilateral multilocular-solid ovarian mass, the specific diagnosis of granulosa cell tumor can be made with high accuracy.

Introduction

Ollier disease (OD) is the most common enchondromatosis subtype, first described in 1899 [1]. It is defined by the presence of multiple enchondromas with asymmetric distribution. Enchondromas are benign and usually consist of asymptomatic hyaline cartilage forming neoplasms in close proximity to growth plate cartilage in the metaphyses and diaphyses of the short and long tubular bones of the limbs. If any hemangioma is additionally detected, the patient is diagnosed with Maffucci syndrome [2].

OD is nonfamilial [3] and mostly encountered in early childhood, affecting both sexes equally, causing severe angular deformities or linear growth discrepancies of the affected bones. The estimated prevalence of OD is 1/100,000 [4]. The diagnosis is based on clinical findings and imaging. Histological analysis is mainly used if malignant transformation in chondrosarcoma (CS) is suspected. Malignant transformation of enchondromas towards chondrosarcoma is estimated to occur in up to 40% of the patients [5] and most frequently occurs in long tubular and flat bones. The first warning symptom is usually a pain followed by palpable mass [6]. In addition to the risk of developing skeletal malignant lesions, Ollier patients also seem to have an increased risk for the development of nonskeletal malignancies, especially intracranial tumors of glial origin and juvenile granulosa cell tumor [3].

This brief report of a case of juvenile granulosa cell tumor associated with Ollier disease is only the 11th such case to be documented in the literature so far (Table 1) [6–15]. Moreover, to

* Corresponding author. Gynecologic Oncology Center, Department of Obstetrics and Gynecology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Apolinarska 18, 128 51 Prague 2, Czech Republic.
E-mail address: daniela.fischerova@seznam.cz (D. Fischerova).

http://dx.doi.org/10.1016/j.tjog.2017.02.002

Table 1
Review of Juvenile granulosa cell tumor (GCT) associated with multiple enchondromatosis (Ollier's disease).

Authors	Initial symptoms of ovarian tumor	Age of patient at diagnosis	Management of ovarian tumor	Follow-up	Y of publication
Sugyima et al [7]	Pubertas preacox	3	LSO	No recurrence (10 y)	1983
Tamimi and Bolen [8]	Abnormal vaginal bleeding, amenorrhea	15	RSO	No recurrence (6 mo)	1984
Pounder et al [9] [b]	Amenorrhea	15	Right oophorectomy	No recurrence (8 y)	1985
	Amenorrhea and lower abdominal pain	22	Left oophorectomy	No recurrence (1 y)	
Vaz and Turner [10]	Pubertas preacox	8	RSO	No recurrence (7 wk)	1986
Schwartz et al [6]	NA	17	NA	No recurrence (19 y)	1987
Velasco-Oses et al [11]	Pubertas preacox	6	RSO	No recurrence (7 y)	1988
Le Gall et al [12]	Abnormal vaginal bleeding	12	RSO	NA	1991
Asirvatham et al [13] [a]	Pubertas praecox	4	Left oophorectomy Bone tumor surgery (left fibula)	No recurrence of ovarian tumor and chondrosarcoma (5 y)	1991
Gell et al [14]	Abdominal discomfort	13	RSO	No recurrence (1 y)	1998
Rietveld et al [15]	No symptoms	36	LSO	NA	2009
Burgetova et al[a] Current report	Pelvic pain	22	RSO Bone tumor surgery (right femur)	No recurrence of ovarian tumor & chondrosarcoma (4 y)	2016

CS = chondrosarcoma; GCT = granulosa cell tumor; LSO = left salpingoophorectomy; NA = not available; Pubertas praecox = Latin term of precocious puberty; RSO = right salpingoophorectomy.
[a] Ollier disease associated with GCT where malignant transformation of enchondromatosis was documented.
[b] Patients presenting with asynchronous bilateral juvenile GCT (aged 15 years and 22 years).

our best knowledge this is the second case published in literature where malignant transformation of enchondroma was documented in a patient with Ollier disease associated with granulosa cell tumor (GCT). The first case was published by Asirvatham et al in 1991 [13].

Case report

A 22-year-old patient with Ollier disease (Figure 1) first diagnosed at 6 months of age was referred for a gynecological transvaginal ultrasound because of pelvic pain and a palpable ovarian mass right-side. The sonographer described a well-encapsulated multilocular-solid tumor 113 mm × 95 mm × 90 mm, with intracystic fluid and moderate vascularity in the solid portion of the tumor originating from the right ovary (Figure 2). No signs of increased estrogen production such as endometrial bleeding were clinically manifested.

Laparoscopic unilateral salpingoophorectomy on the right was performed in the local hospital. The histological report revealed granulosa cell tumor (Figure 3) according to the International Federation of Gynecology and Obstetrics (FIGO) Stage IC [16].

The patient was referred for consultation to our Gynecologic Oncology Center, Department of Obstetrics and Gynecology, First Faculty of Medicine, Charles University. During physical examination of this patient, an asymmetrical involvement of the extremities caused by multiple enchondromas was discovered. The patient asserted that she experienced a marked pain during walking on the right side. As no fracture could be diagnosed, the pain was most probably caused by the palpable bulge on the ventral part of the proximal femur.

Transabdominal and transvaginal ultrasound was made by experienced sonographer with a normal abdominal finding. In the uterus a slightly inhomogenous endometrium of 9 mm thickness in the late secretory phase was observed. In the right groin a large soft-tissue tumor of 91 mm × 60 mm × 63 mm was found (Figure 4). The tumor had a solid structure with anechoic necrotic portion, sporadic vascularity, and calcification. No invasion of tumor in the adjacent organs was visible. Whole body computer tomography was performed. The radiologist described the tumor as a soft tissue component of an enchondroma originating from the trochanter tuberosity with the osteolysis. It strongly indicated malignant transformation of enchondroma (Figure 5).

From the gynecological side a hysteroscopy was conducted to exclude the possibility of endometrial pathology caused by increased estrogen production. The result was a normal macroscopic and histological finding. The original specimens (i.e., paraffin embedded blocks) from ovarian juvenile GCT were referred to an experienced pathologist for a second opinion, which proved juvenile GCT (Figure 3). The patient was presented to our tumor board and no additional surgical staging procedure or systematic treatment regarding the GCT was recommended, except for a

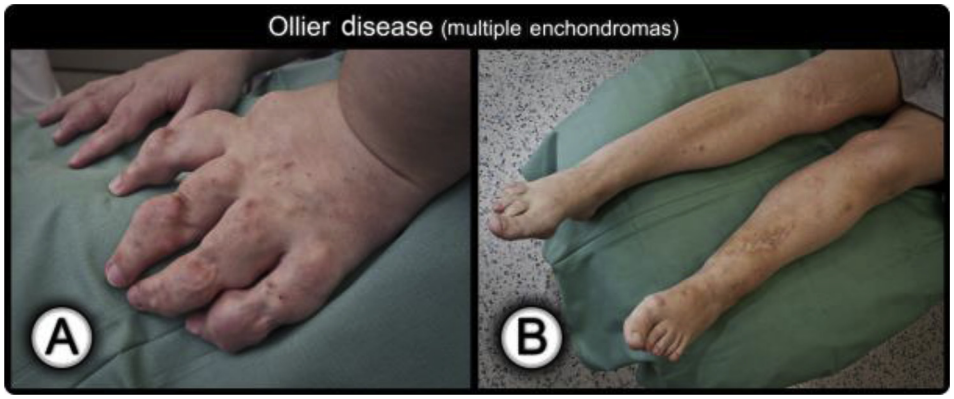

Figure 1. A 22-year old patient with Ollier disease. (A) Left hand showing deformities due to multiple enchondromas and finger enlargement; (B) deformities of the toes and multiple scars following surgical procedures due to multiple osteotomies and length prolongation.

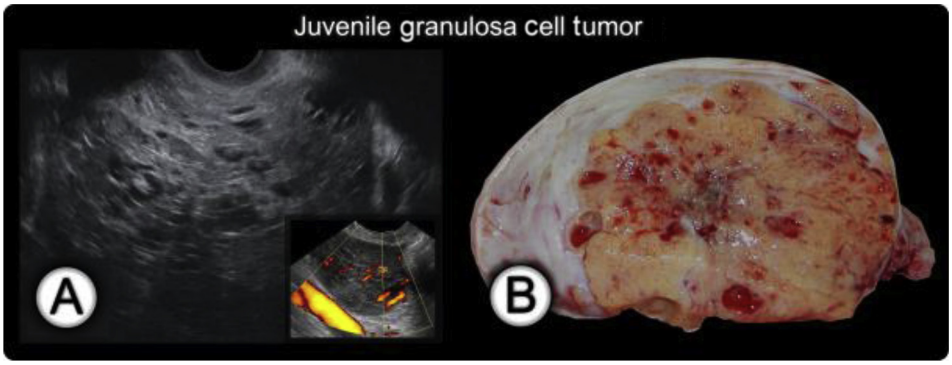

Figure 2. Juvenile GCT of the right ovary. (A) An ultrasound transvaginal scan of characteristic "sponge-like" appearance of multilocular-solid tumor with innumerable cystic spaces filled with low-level fluid (i.e., blood). Increased vascularity in solid portion of tumor is demonstrated on power Doppler; (B) gross tumor appearance with multiple blood-filled cysts within the tumor. The solid component is typically yellow-tan. GCT = granulosa cell tumor.

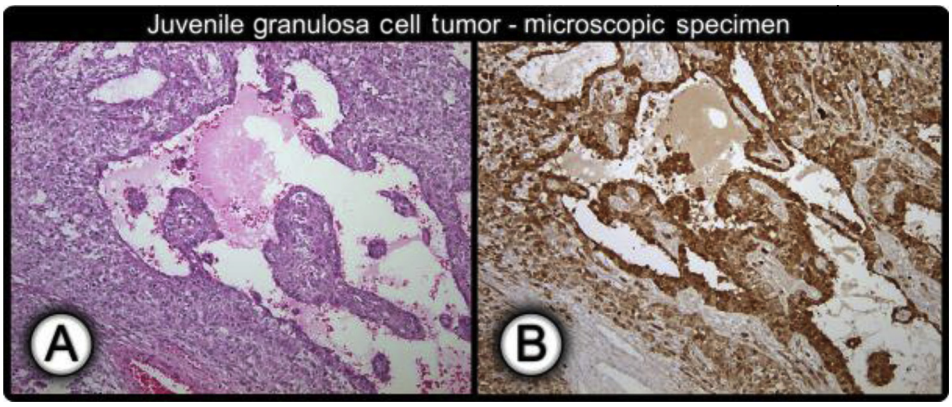

Figure 3. Juvenile granulosa cell tumor of the right ovary. (A) Histological finding of granulosa tumor cells with rounded nuclei arranged in solid and follicular pattern (hematoxylin and eosin stain, × 100); (B) tumor cells showing diffuse immunohistochemical positivity for calretinin (calretinin stain, × 100).

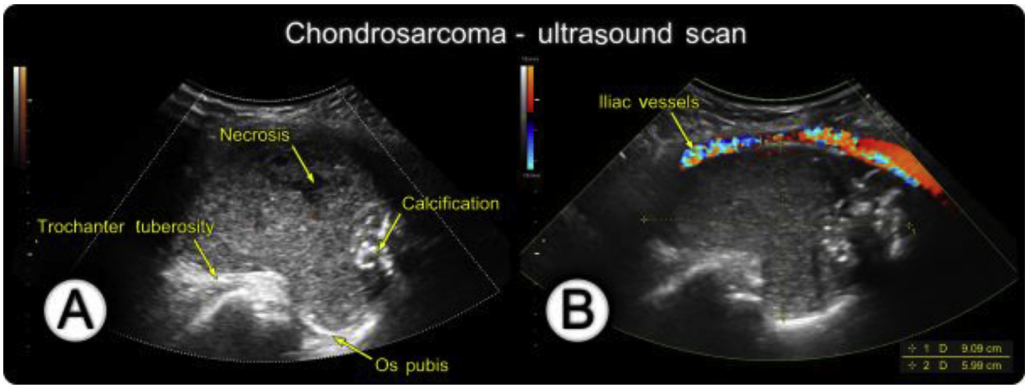

Figure 4. Ultrasound scan of chondrosarcoma. (A) A hypoechogenic solid tumor with mild vascularity, hypoechogenic necrotic portion and calcification; (B) the external illiac vessels bulged by the tumor on color Doppler.

detailed and adequately long follow-up based on expert ultrasound provided at our Center.

The patient was referred to the Bone Tumor Center, Orthopedic Clinic, Bulovka Hospital, First Faculty of Medicine, Charles University. She underwent a wide resection of the extraosseal soft tissue tumor and the major part of the lesser trochanter followed by curettage sampling of the greater trochanter and cement closure of the trochanteric cavity. Final histology revealed a chondrosarcoma Grade 2 detected only in the extraosseal tumor part with tumor-free resection margins, whereas in the curetted tissue of the greater trochanter only enchondromas was proved (Figure 6). The patient is being followed in the bone tumor center, in accordance with guidelines for the follow-up of conventional chondrosarcoma. Her last clinical visit in the Bone Tumor and our Gynecological Oncology Center was in February 2016 (4 years after first diagnosis and oncological treatment) with signs of complete remission.

Discussion

The specific preoperative diagnosis of the juvenile GCT is possible if clinical and imaging clues are combined. The mean age of

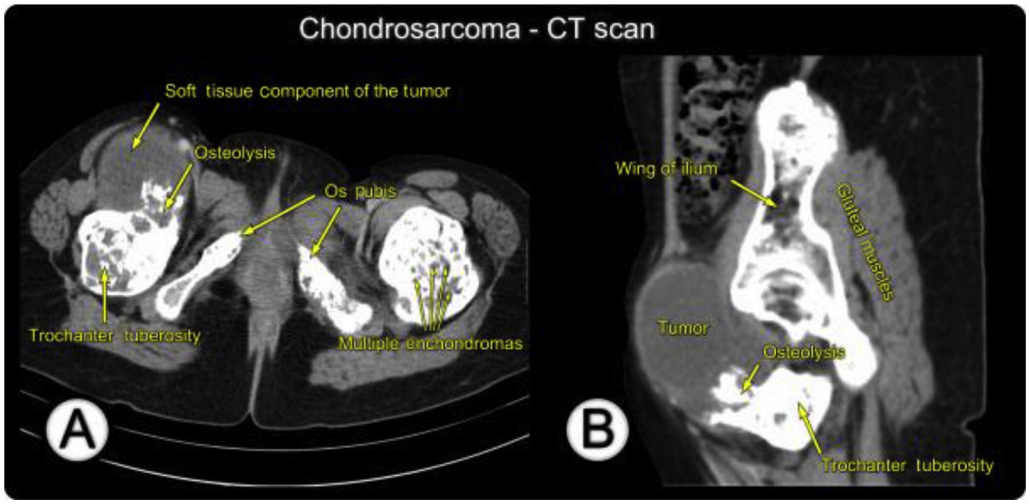

Figure 5. Computer tomography scan of multiple enchondromas and chondrosarcoma. (A) Transverse section; (B) sagittal reconstruction. Multiple enchondromas cause changes in bone structures and bone deformities. Chondrosarcoma growing from the trochanter tuberosity of the right femur.

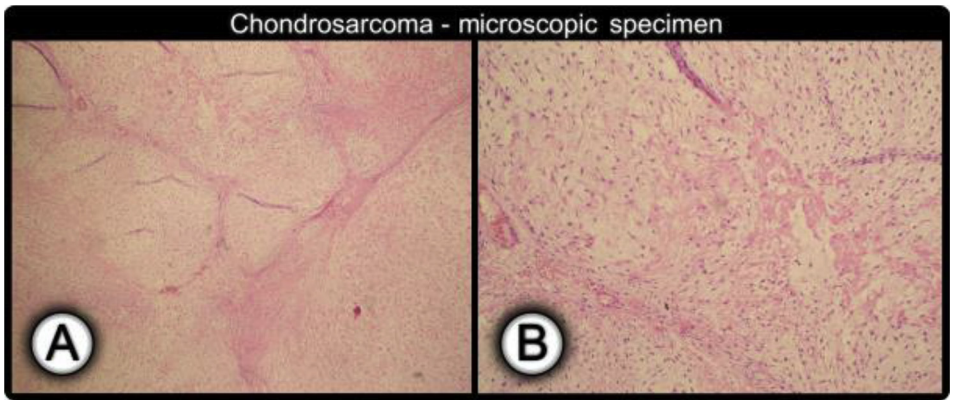

Figure 6. Pathological specimen from chondrosarcoma Grade 2. (A) Note the irregularly shaped lobules of cartilage (hematoxylin and eosin stain, × 40); (B) tumor cells with mild nuclear atypia located within myxoid stroma.

patients with juvenile GCTs is 13 years. The production of estrogen by tumor cells manifests clinically as pseudoprecocious puberty in premenarchal girls and as endometrial pathology (endometrial bleeding, endometrial hyperplasia, polyps, or well differentiated endometrial carcinoma etc.) in fertile women. On ultrasound the granulosa cell tumor is characterized as a typically large unilateral predominantly multilocular-solid tumor with a so called "swiss-cheese" or "sponge-like" appearance due to large numbers of small locules (> 10) [17]. The echogenicity of the cyst content is most often of a mixed or low level reflecting the presence of blood. Unlike epithelial neoplasms, GCTs do not have intracystic papillary projections, the solid portions of the tumors manifested a moderate or high color content on color Doppler examination [8]. If there is an association with multiple enchondromatosis, the differential diagnosis of ovarian tumor should be unmistakable.

Sex cord-stromal tumors represent ~ 8% of ovarian neoplasms and among them the GCTs are the most common [18]. GCTs are derived from the primordial sex cords (i.e., from the granulosa cells that surround the developing follicles). Two types are distinguished histologically: adult GCT (95%) and juvenile GCT (5%), the latter is more common than adult GCTs in patients younger than 30 years old. They share a similar gross appearance, are usually unilateral, Stage I estrogen secreting tumors. Although GCTs have the potential for clinically malignant behavior, Stage I tumors usually have an excellent prognosis. In addition, juvenile GCT is less likely than adult GCT to recur after simple unilateral salpingo-oophorectomy, so this may be an acceptable alternative to more extensive surgery in young women. Based on this fact, no additional surgical and/or systematic treatment regarding the juvenile granulosa cell tumor was completed in this patient.

However, because of the association of the juvenile GCT with Ollier disease, there was an increased risk of a malignant transformation of enchondromas into secondary chondrosarcomas in this 22-year-old patient based most probably on an as yet unidentified and more profound genetic defect. The risk was even higher because of the early onset of Ollier disease and chronic irritation of enchondromas due to recurrent osteomyelitis and prolongation of long bones. In addition, the risk of developing chondrosarcoma is further increased when enchondromas are located in the pelvis (odds ratio, 3.8; $p = 0.001$) as in this patient [5]. In the literature, malignant transformation in preexisting enchondromatosis was estimated between 20% and 45.8%, the age of patients with a secondary chondrosarcoma ranged from 10 years to 69 years (an average age approx. 52 years) [19]. The distinction of a solitary enchondroma from a solitary low-grade chondrosarcoma on a conventional radiograph may be difficult. The radiological features of chondrosarcomas include cortical destruction and/or soft tissue involvement. Dynamic contrast-enhanced MRI is more

helpful in this regard [20], but no one imaging method may define the border between benign and malignant chondrogenous tissue. A biopsy should be completed to plan an individual surgical approach. However, the distinction between enchondroma and chondrosarcoma is also difficult in histology with a high level of interobserver variability [6,21–23]. In this patient the diagnosis of malignancy was highly suspicious based on clinical symptoms and imaging. After a detailed consultation the patient opted for the less radical procedure instead of radical tumor resection with a total femur reconstruction. She was aware that the radical procedure would be followed as the second step of the procedure in the case that no tumor-free margin and/or of positive curettage in histology findings. The histological report revealed an Evans Grade 2 chondrosarcoma [24] only in soft tissue tumor with adequate tumor free margin and negative curettage and so the conditions for the more limited surgery were met. The prognosis of chondrosarcoma associated with Ollier disease seems to be similar to the primary chondrosarcoma, nevertheless the femur is the most risky location [5]. In the first case of Ollier disease associated with GCT and complicated by malignant transformation of enchondroma to CS [13], 5 years after treatment there was no evidence of recurrence of either CS nor ovarian tumor. In our second case complete clinical remission lasts 4 years.

In conclusion this case report presents an association of multiple enchondromatosis (Ollier disease) complicated by malignant transformation of enchondroma in femur into chondrosarcoma with nonskeletal malignancy (ovarian juvenile granulosa cell tumor) in a 22-year old patient. Although Ollier disease is rare and its association with juvenile granulosa cell tumor has been noted sporadically, it is important to recognize that when the female patient presents with enchondromatosis and a large unilateral multilocular-solid ovarian mass, the specific diagnosis of ovarian tumor can be made with high accuracy.

Conflicts of interest

Daniela Fischerova discloses funding received from the following organisations: National Institutes of Health, Wellcome Trust, and Howard Hughes Medical Institute.

Acknowledgments

This work was supported only by the Ministry of Health, the Czech Republic and by Charles University in Prague (Internal Grant Agency of the Ministry of Health, the Czech Republic, grants No. NT13070 and RVO VFN64165; Charles University in Prague-UNCE 204024 and PRVOUK-P27/LF1/1). Thanks to Adam Preisler from the Faculty of Architecture, Czech Technical University in Prague, for providing the graphic design of the images.

References

[1] Ollier L. Dyschondroplasie. Lyon Med 1900;93:23–5.
[2] Mafucci A. Diu n caso di enchondroma ed angioma multiplo: contribuzione alla genesi embrionale dei tumori. Mov Med Chir Nap 1881;3:399–412 [Italian].
[3] Pansuriya TC, Kroon HM, Bovee JV. Enchondromatosis: insights on the different subtypes. Int J Clin Exp Pathol 2010;3(6):557–69.
[4] Silve C, Juppner H. Ollier disease. Orphanet J Rare Dis 2006;1:37.
[5] Verdegaal SH, Bovee JV, Pansuriya TC, Grimer RJ, Ozger H, Jutte PC, 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.
[6] Schwartz HS, Zimmerman NB, Simon MA, Wroble RR, Millar EA, Bonfiglio M. The malignant potential of enchondromatosis. J Bone Joint Surg Am 1987;69(2):269–74.
[7] Sugiyama MKY, Miyoshi T, Ogawa S. *In vivo* and *in vitro* steroid bio-synthesis by ovarian juvenile granulosa cell tumor of a girl with Ollier's disease. Acta Gynaecol Obstet Jpn 1983;35:2185.
[8] Tamimi HK, Bolen JW. Enchondromatosis (Ollier's disease) and ovarian juvenile granulosa cell tumor. Cancer 1984;53(7):1605–8.
[9] Pounder DJ, Iyer PV, Davy ML. Bilateral juvenile granulosa cell tumours associated with skeletal enchondromas. Aust N Z J Obstet Gynaecol 1985;25(2):123–6.
[10] Vaz RM, Turner C. Ollier disease (enchondromatosis) associated with ovarian juvenile granulosa cell tumor and precocious pseudopuberty. J Pediatr 1986;108(6):945–7.
[11] Velasco-Oses A, Alonso-Alvaro A, Blanco-Pozo A, Nogales Jr FF. Ollier's disease associated with ovarian juvenile granulosa cell tumor. Cancer 1988;62(1):222–5.
[12] Le Gall C, Bouvier R, Chappuis JP, Hermier M. Ollier's disease and juvenile ovarian granulosa tumor. Arch Fr Pediatr 1991;48(2):115–8.
[13] Asirvatham R, Rooney RJ, Watts HG. Ollier's disease with secondary chondrosarcoma associated with ovarian tumour. A case report. Int Orthop 1991;15(4):393–5.
[14] Gell JS, Stannard MW, Ramnani DM, Bradshaw KD. Juvenile granulosa cell tumor in a 13-year-old girl with enchondromatosis (Ollier's disease): a case report. J Pediatr Adolesc Gynecol 1998;11(3):147–50.
[15] Rietveld L, Nieboer TE, Kluivers KB, Schreuder HW, Bulten J, Massuger LF. First case of juvenile granulosa cell tumor in an adult with Ollier disease. Int J Gynecol Pathol 2009;28(5):464–7.
[16] Benedet JL, Bender H, Jones 3rd H, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstetrics 2000;70(2):209–62.
[17] Van Holsbeke C, Domali E, Holland TK, Achten R, Testa AC, Valentin L, et al. Imaging of gynecological disease (3): clinical and ultrasound characteristics of granulosa cell tumors of the ovary. Ultrasound Obstet Gynecol 2008;31(4):450–6.
[18] Greaves M, Culligan DJ. Blood and bone marrow. In: Underwood JCE, editor. General and systematic pathology. 4th ed. London: Churchill Livingstone; 2004. p. 615–72.
[19] Herget GW, Strohm P, Rottenburger C, Kontny U, Krauss T, Bohm J, et al. Insights into enchondroma, enchondromatosis and the risk of secondary chondrosarcoma. Review of the literature with an emphasis on the clinical behaviour, radiology, malignant transformation, and the follow up. Neoplasma 2014;61(4):365–78.
[20] Choi BB, Jee WH, Sunwoo HJ, Cho JH, Kim JY, Chun KA, et al. MR differentiation of low-grade chondrosarcoma from enchondroma. Clin Imaging 2013;37(3):542–7.
[21] Mirra JM, Gold R, Downs J, Eckardt JJ. A new histologic approach to the differentiation of enchondroma and chondrosarcoma of the bones. A clinicopathologic analysis of 51 cases. Clin Orthop Relat Res 1985;(201):214–37.
[22] Eefting D, Schrage YM, Geirnaerdt MJ, Le Cessie S, Taminiau AH, Bovee JV, et al. Assessment of interobserver variability and histologic parameters to improve reliability in classification and grading of central cartilaginous tumors. Am J Surg Pathol 2009;33(1):50–7.
[23] Superti-Furga A, Spranger J, Nishimura G. Enchondromatosis revisited: new classification with molecular basis. Am J Med Genet C Semin Med Genet 2012;160c(3):154–64.
[24] Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. Cancer 1977;40(2):818–31.