Two cases with Familial Tumoral Calcinosis in Bulgaria

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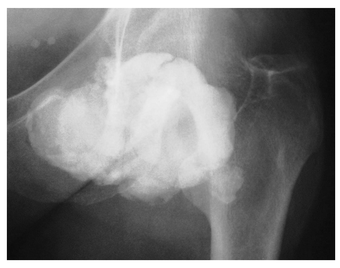

INTRODUCTION

Familial tumoral calcinosis (FTC) is a rare autosomal recessive disorder characterized by the progressive deposition of calcified masses in cutaneous and subcutaneous tissues, which results in painful ulcerative lesions and severe skin and bone infections and has mild biochemical phenotype in heterozygotes /14, 17, 26/ Two major types of FTC have been recognized: hyperphosphatemic FTC (HFTC) and normophosphatemic FTC (NFTC) .

The NFTC result from mutations in SAMD9 gene.The data suggest that SAMD9 is involved in the regulation of extraosseous calcification, a process of considerable importance in a wide range of diseases as common as atherosclerosis and autoimmune disorders.

HFTC is caused mainly by two genes GALNT3 and FGF23.The GALNT3 gene was mapped to 2q24-q31 /26/ . The gene encodes a UDP-N-acetyl-alfa-D-galactosamine-polypeptide –N-acetylgalactosaminyltransferase 3 /ppGaNTase-T3/GALNT3 responsible for initiating mucin-type O-glycosylation of proteins including FGF23, suggesting that defective posttranslational modification underlies this disorder. The FGF23 gene was mapped at 12p13.3 /2, 5, 16/. The inadequate production of biologically active FGF23, required for normal phosphate reabsorbtion leads to hyperphosphatemia due to enhanced renal phosphate retention, normal or elevated 1,25 dihydroxivitamin D /calcitriol/ , and by ectopic calcification (periarticular or dermal)/15/ .

The aim of our work was to describe the clinical picture of Bulgarian patients with FTC and conclude that this rare disease exist in our country.

MATERIALS AND METHODS

The authors described two unrelated patients from the Turkish minority and Bulgarian Mohammedan affected by Tumoral calcinosis diagnosed at University Hospital of Orthopedics and Traumatology “Prof. Boicho Boichev “ .There were used anthropometry, family history, history of disease , orthopedical status , Rentgenography , CAT, MRI ,Scintigraphy, Echography of abdomen, biochemical investigations (blood count, coagulation status, total protein, albumin, glucose, urea, creatinine, uric acid, Ca, P, electrolytes ASAT, ALAT, GGT, AP), investigation of urine (protein, sugar, ketobodies, bilirubin, urobilinogen, creatinine clearance), histological investigation.Patients had consultations with a pediatrician, neurologist and cardiologist.

DESCRIPTION OF THE CASES

S.M.B-a 15 year`s old girl, Bulgarian Mohammedan, from first pregnancy and normal delivery.She has a healthy sister . She was admitted to the clinic for large tumoral mass .The disease began at the age of 6 year`s old with tumoral mass of the right shoulder successfully cured after repeated /2-fold/ excision. At the age of 11, free of pain swelling appeared on the medial surface of the left ankle, wherefrom following excision , a lime –like pasty material was evacuated in the in the left hip region, which appeared two years ago.At 13 year`s old appeared a tumoral mass in the left hip region which grew up visibly for 2 years and became painful in the last 8 months, resulting in progression restriction of the hip motion.Excision was undertaken 3 times, but invarably the formation relapsed.The physical examination showed normal mental and psychomotor development , normal height and weight.Ambulation without using assisting devices with slight left side claudication, rather pronounced when walking on rough surface.The left hip had visible deformity due to edema with unaltered overlying skin , except for the operative scars.In the proximal third of the left thigh on the anterior and partly lateral part , a painless tumor formation with size 20/12/8 is palpated.The skin was not involved and revealed no signs of systematic disease.The mass was lobulated of hard consistence, relatively mobile to bone and fixed in the soft tissues.The hip movement in the area were restricted. Dense homogenous calcified masses were detected around the left hip on X-rays.They were lobulated by radio-translucent septae and resembled to conglomerates.The buttock muscles were partly infiltrated with the major trochanter in intimate contact with them.The scintigraphy showed markedly expressed accumulation –of radiopharmacon-up to 270 percent.The echography showed no calcification in the viscera.The routine biochemical investigations of blood / glucose, electrolyte,tryglicerides , SGOT, SGPT, AP, CK, GGT, glucose tolerance test and thyroid function were normal and urine / protein, glucose, ketobodies, bilirubin, urobilinogen, sediment were in normal values.The ESR was strongly elevated.The values of Ca++2.0 mmol/l , ionized calcium 0.8 mmol/l and inorganic phosphorus-1.12 mmol/l were in normal values too.Treatment –the patient was operated and the formation was extirpated.A lobulated tumorous mass weighting 2.2 kg, infiltrating gluteus medius , tensor fasciae latae and the proximal end of vastus lateralis was found, On section it consisted of fibrous connective tissue with numerous small unequal cysts.Some of the later contained grey-yellowish fluid , while others contained pasty similar to talkc material, which analysis showed phosphate and carbonate calcium salts.Microscopically the cystic zones contained amorphous , granulated material, yellowish-brownish in the hematoxin-eosin sections and showing strongly positive von Kossa reaction.Palissade cells with increased amount of alkaline phosphatase were established in the periphery of the cystic zones.A multitude of polynucleate cells , histiocytes, chronic inflammatory cells foci of necrosis and hemosiderin were also observed.The inactive zones present edematous , granulomatous foci or dense fibrous tissue with chronic inflammatory infiltration.We recommended a low calcium and phosphorus diet and oral antiacid treatment./suspension of aluminium-magnesium/Seven years later the patient was free of complaints and was no evidence for recurrence.

R.R.E.03.04.53,Turkish minority, History of disease No 593/08, University Hospital of Orthopedics and Traumatology ,Gorna Bania, Sofia, Bulgaria

The family history showed no data for tumoral calcinosis.The patient has thalassemia and supraventricular tachycardia , arterial hypertonia and thrombophlebitis of the right leg in the past. The ophthalmological investigation showed amauvrosis with corneal nubecula , rupture of iris, complicated cataracta of the left eye, bilateral hypermetropia , divergent strabismus of the left eye.

The disease began at the age of 55 year`s old with painful increasing formations in the gluteal region.In the mass of m.gluteus maximus at left was palpable a longitudinal formation with diameter 10cm.The present status showed independent ambulation .In the mass of m.gluteus maximus was palpated a tumoral formation with dense consistence 10/8/7 cm in size , slightly painful at palpation.The motion in the hip joint was extension 0-0-120º, flexion 20-0-20º, rotation 20-0-30º.

The biochemical investigations blood count, ASAT, ALAT, total protein, coagulation status, fibrinogen, glucose, electrolytes, urea, creatinine were in normal values .The calcium and ionizated calcium were in normal ranges too.The echocardiography showed normal structure and function of the heart.The angiological status was normal too.The rentgenography of the hip joint showed coxarthrosis more pronounced at the lower pole of the acetabulum. The rentgenography of the pelvis showed lack of bone changes and a massive calcification in the left gluteal region The rentgenography of spine showed osteoporosis, spondylosis, osteochondrosis at the level L3,4,5 ,S1. The CAT of spine showed enlarged discs, arthrosis changes and relative stenosis of canalis vertebralis at the level of L4-L5, right paramedian disc protrusion at the level of L5-S1 and calcification in the soft tissues in the gluteal region. The MRI coronary, T1W DUAL-FSE, axial T2W/TSE,sagital -T2W/me2d2u showed a large at volume hypo- to anintensed zone in comparison of the muscles in T1 and hyperintensed in T2 pathological mass, localized in the left ischiadic bone and the lower gluteal arteries in the mass of ipsilateral m.gluteus maximus with the engagement of the sacrospinal ligament with expansive growth medially and laterally.The interlesional characteristic of the formation showed centrally localized large at size calcium deposits, solid components and evident fluids at the periphery probably due to necrosis.There was a pronounced mass effect due to the infiltration of the expansion of the formation and the infiltration of the muscles without involvement of the bones and the lower gluteal arteries but with possible infiltration of n.ischiadicus.

The patient was operated . After local excision of the tissue or lesion the formation was resected in the region of the tuber of the ishiadic bone .The tumoral formation was with macroscopic evidence of tumoral calcinosis .The histological investigation showed proliferation of fibrous tissue and fragment of hyalinizated tissue with calcinosis without cell reaction.

DISCUSSION

The diagnosis of the following cases was made on the base of histological findings around the hydroxiapatite deposits , the characteristic X-ray, CAT and MRI findings, the clinical evolution and biological behaviour.The definite diagnosis should be confirmed with molecular analysis .The mutational analysis is important for the exact diagnosis , early recognition of the disorder , for prevention of its complications and for family screening strategies but at present it is not available in our country.The DNA from the second patient was sent to Tel Aviv Sourasky Medical center , Dermatologic department, Israel for DNA analysis and the result is expected.

Before the definite diagnosis Tumoral calcinosis we ruled out all possible cases giving rise to soft tissue calcifications: metastatic, dystrophic and idiopathic.The metastatic calcifications result from impaired calcium or phosphorus metabolism in chronic renal failure, primary hyperparathyreoidism, Vit D intoxication , excessive milk and alkalyzing foods intake and in osteomyelitis , metastatic carcinoma , plasmocytoma and leukaemia/ 3, 4/.The dystrophic calcifications are associated with calcium deposits in previously damaged or devitalized tissues following trauma, ischemia or systemic disease / for exemple vascular, cancer and autoimmune diseases/7, 8, 23/In this group are included too calcifying tenosynovitis and interstitial variants of calcinosis-circumscripted and universal /13/. Idiopathic calcifications are usually present in tumoral calcinosis.On X-rays the calcium deposits showed clearcut lobulated shadows , usually situated on the extensor joint surface with cobblestone appearance, strongly contrasting with the calcifications seen in synovial sarcoma.The underlying bone isn`t changed irrespective of eventually observed cortical impressions.The diagnosis may be suggested by nodular calcifications in conjunction with cystic zones containing turbid fluid and sediment deposits/3 /.The CAT and MRI afford additional information on the interrelations between calcium deposits and contiguous bone , which in turn responds in a different pattern which is observed in our cases.Scintigraphy is useful in detecting other foci of this kind. Macroscopically the mineral deposit exhibit different size –the biggest may reach 15 cm./ 21 /A continous fibrous pseudocapsule whose septa filled with clear or milk like fluid is seen similar to our cases.The first case described by us present 20 cm in diameter and weight 2.2 kg is the largest one published so far.The calcium deposits become evident under microscopic study. Slavin, 1993 /22 / concluded that tumoral calcinosis is triggered by bleeding, followed by aggregation of foamy histiocytes. These, in turn, are transformed, with participation of collagenolysis, into cystic cavities lined by osteoclast-like giant cells and histiocytes, resulting in lesions resembling adventitious bursae. Movement and friction resulting from the periarticular location of the lesions were thought to be key to this transformation. Special techniques /von Kossa/ contribute to detect the presence of calcium in giant cells of the granuloma surrounding necrotic calcium foci.The polymorphous inflammatory granuloma itself is made up of giant polynucleate, plasmocytic and hysticytic cells.Somewhere in the neighboring collagen are discovered elastic fibers in a state of degeneration.In the numerous necrotic zones are established many rounded or oval calcium depots like the observed changes in the first case.In its inactive phase a dense hypocellular tissue circumscribes the lesion like the observation in the second case described by us. Electron microscopically two types of cells may be seen :mono –and polynuclear macrophages and fibroblastic type cells.There are no signs of damage to the microvessels or the interstitial collagen attributable to the physiopathological process.The X-ray microanalysis and electron diffraction consider the deposits to be hydroxiapatite./10/ In the first described case the erythrocyte sedimentation rate was strongly accelerated as eventually observed in HFTC but the calcium and phosphorus were in normal values as seen in NFTC.Although usually the disease becomes manifested with numerous foci, most of the reportsfrom Africa describe isolated locations , mainly around large joints-hip, elbow, shoulder and rather seldom hands, feet, and knee/ 6, 7, 13, 19/.In the first case were affected three joints but never simultaneously.On X-rays and histologically our reported patients were presenting calcium deposits with numerous active zones similar to the describe in literature/8/The lack of evidence of visceral deposits differentiate the condition from universal calcinosis/12/.The widespread involvements of periarticular soft tissues without presence of a systemic collagen disease differentiate it from calcinosis circumscripta.The normal blood calcium ruled out the possibility of metastatic calcinosis.The analysis of literature data showed common and early relapses most of them within the first few months.The large resection of the involved tissue does not ruled out relapse with ensuing exulceration of the overlying skin and infection/1, 6, 13, 18, 20, 25 / .We have conclusive evidence that total resection is really difficult .Although apparently capsulated calcinosis is devoid of a true capsule differentiating it from the surrounding tissues.One is surprised of the capacity of the tumor to infiltrate adjacent tissues by spreading out not only between the muscles , but also in between muscle fibers and tendons. The recommended therapy with a low calcium and phosphorus diet and intake of phosphate –binding aluminium hydroxide antacids showed a good effect. After the beginning of treatment both patients hadn`t relapses of the disease./9, 11, 18, 24/

CONCLUSION

The authors recommend molecular genetic analysis of GALNT3 and FGF23 gene for exact diagnosis and genetic counseling of patients with FTC

The early diagnosis and treatment with low calcium and phosphorus diet and phosphate binding aluminium hydroxide antacids could prevent complications and relapse of the disease

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