European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases
Newsletter

Issue 20 – January 2010

Editorial News

INSIDE THIS ISSUE:

Dear Members of the Working Group,

please find enclosed the 20th issue of our Newsletter.

In addition to the 'clinical case of the month' and the 'paper of the month' you will find within this issue the case resolution from the December case.

For the first time the 'paper of the month' includes a list of considerations, which we think could be matter of debate on the web, please let us know your opinion or comments.

On the last page of the newsletter you will find some recommendations for further reading with a list a recently published papers in the field of our WG……

Best wishes for all of you.

S. Pankuweit

The paper of the month:

Implications of Hypertrophic Cardiomyopathy Transmitted by Sperm Donation

Maron BJ, Lesser JR, Schiller NB, Harris KM, Brown C, Rehm HL. JAMA. 2009;302:1681-4

Just a curiosity?

Presented by Eloisa Arbustini, Alessandra Serio, Michele Pasotti, Fabiana I Gambarin, Luigi Tavazzi*
Centre for Inherited cardiovascular Diseases, IRCCS Foundation Policlinico San Matteo, Pavia; *GVM Care and Research, Cotignola (Ravenna), Italy. e.arbustini@smatteo.pv.it

In the above issue of JAMA, Maron et al. reported the clinical circumstances and implication of hypertrophic cardiomyopathy (HCM) transmitted by sperm donation to recipients. (Voluntary sperm donation through a US Food and Drug Administration–approved tissue bank).

The case

The authors report the case of an asymptomatic 23-year-old man who had no personal knowledge of underlying heart disease and who underwent standard testing that was negative for infectious diseases and repeatedly donated sperm over a 2-year period (1990-1991).

Diagnosis of HCM in the donor

The donor was later known (in 2005) to carry a novel *MYH7* mutation that caused HCM, after an offspring was clinically diagnosed with this disease. Of the 24 children known to be offspring of the donor, including 22 who were products of fertilization via sperm donation and 2 conceived by the donor's wife, a total of 9 genetically affected offspring, 2 to 16 years of age and 6 males, have been identified with HCM (2005-2009).

Phenotype expression

9/22 children (41%) were carriers of the paternal mutation (age 2-16 years; 6 males):

- one has functional limitation with exertional chest pain and fatigue,
- one experienced presyncope and palpitations,
- the other 7 remain asymptomatic.

HCM phenotype in offspring

Two of the living offspring (the above two children with symptoms) have phenotypic evidence of HCM show extreme LV wall thickness involving the ventricular septum of 30mmand 34mm. One of these children has received a prophylactically implanted cardioverter-defibrillator for prevention of sudden death.

Another genetically affected offspring, died at 2.5 years of age of obstructive HCM (ventricular septal thickness, 22 mm) and progressive heart failure while awaiting transplant.

Six of the 9 genetically affected children do not currently show LV hypertrophy as assessed by 2-dimensional echocardiography at ages 7, 7, 11, 15, 15, and 16 years (mean age, 12 years), although other findings were consistent with phenotypic expression, including mild systolic motion of the mitral valve in one (IV-6) and an abnormal electrocardiogram in the other (IV-3).

Paternal HCM phenotype

The father (III-3) showed segmental LV hypertrophy (thickness, 18 mm) of the posterior (inferior) LV. The electrocardiogram showed T-wave inversion (most prominent in V4-V6), and left atrial enlargement.

CMR showed extensive delayed enhancement consistent with myocardial fibrosis that was largely confined to the hypertrophied region of LV.

Non-mutated offspring

Hypertrophy was absent by echocardiography in each of the 9 offspring with negative genetic testing.

Conclusions

This case underscores the potential risk for transmission of inherited cardiovascular diseases through voluntary sperm donation, a problem largely unappreciated by the medical community and agencies regulating tissue donation. Recommendations include improved screening guidelines for donors to exclude cardiovascular diseases such as HCM and consideration for 12-lead electrocardiograms.

CONSIDERATIONS

A) Transmission of a genetic disease by sperm donation

This case fist documents that a genetically determined cardiac disease can be transmitted via sperm donation. A case of Fragile X has also been reported (2). A symptomless donor can be unaware of his disease at the time of donation, especially if cardiological investigations have not been performed. ECG and ECHO are non-obligate tests for apparently healthy donors; a simple ECG control could be sufficient for suspecting HCM, as suggested by the authors. In the setting of cardiovascular diseases, the risk of transmission of an autosomal dominant disease with late penetrance or symptomless exists and is proportional to the prevalence of the disease itself. HCM is the most prevalent autosomal dominant cardiovascular disease in the general population. Other autosomal dominant cardiomyopathies with age-dependant phenotype expression are less prevalent (DCM 1:2500, ARVC 1: 5000) and frequently the family history documents cardiovascular events or affected family members.

B) Hypertrophic cardiomyopathy (HCM)

- The HCM is a high-prevalence disease (1.500), familial in more than 70% of the cases, and transmitted as autosomal dominant disease. This is a prevalence datum confirmed in more studies in the young- mid-age population.
- HCM may be asymptomatic or clinically non-manifested, especially considering the age-dependant phenotypes and the possibility of low penetrant mutations.
- The clinical impact of HCM may vary in different countries and races, with minor negative affects in case of HCM associated with mutation, for example, of the MYBPC3 gene.
- The risk of transmission by sperm donation exists.

C) Medically assisted procreation and sperm donation

- The rate of medically assisted procreation and sperm donation to achieve pregnancy, either in the absence of a male partner or in the presence of fertility problems is increasing. Data from media indicate a number of anonymous donor inseminated births per year of 30,000. An unpublished survey conducted by the AATB suggests that a more likely rate would be 4,000 to 5,000 donor-inseminated births per year. By extrapolating this annual figure, the total number of anonymous donor inseminated births is estimated to be less than 130,000 over the last 30 years. Considering the prevalence of HCM along with the possibility of repeated donations for years, the minimal number of expected HCM is 260 over the last 30 years. One may say that HCM is a "benignant" genetic disease as compared with more severe genetic diseases; however, at least 10% of patients develop malignant complications.

CONSIDERATIONS

A) Transmission of a genetic disease by sperm donation

This case fist documents that a genetically determined cardiac disease can be transmitted via sperm donation. A case of Fragile X has also been reported (2). A symptomless donor can be unaware of his disease at the time of donation, especially if cardiological investigations have not been performed. ECG and ECHO are non-obligate tests for apparently healthy donors; a simple ECG control could be sufficient for suspecting HCM, as suggested by the authors. In the setting of cardiovascular diseases, the risk of transmission of an autosomal dominant disease with late penetrance or symptomless exists and is proportional to the prevalence of the disease itself. HCM is the most prevalent autosomal dominant cardiovascular disease in the general population. Other autosomal dominant cardiomyopathies with age-dependant phenotype expression are less prevalent (DCM 1:2500, ARVC 1: 5000) and frequently the family history documents cardiovascular events or affected family members.

B) Hypertrophic cardiomyopathy (HCM)

- The HCM is a high-prevalence disease (1.500), familial in more than 70% of the cases, and transmitted as autosomal dominant disease. This is a prevalence datum confirmed in more studies in the young- mid-age population.
- HCM may be asymptomatic or clinically non-manifested, especially considering the age-dependant phenotypes and the possibility of low penetrant mutations.
- The clinical impact of HCM may vary in different countries and races, with minor negative affects in case of HCM associated with mutation, for example, of the MYBPC3 gene.
- The risk of transmission by sperm donation exists.

C) Medically assisted procreation and sperm donation

- The rate of medically assisted procreation and sperm donation to achieve pregnancy, either in the absence of a male partner or in the presence of fertility problems is increasing. Data from media indicate a number of anonymous donor inseminated births per year of 30,000. An unpublished survey conducted by the AATB suggests that a more likely rate would be 4,000 to 5,000 donor-inseminated births per year. By extrapolating this annual figure, the total number of anonymous donor inseminated births is estimated to be less than 130,000 over the last 30 years. Considering the prevalence of HCM along with the possibility of repeated donations for years, the minimal number of expected HCM is 260 over the last 30 years. One may say that HCM is a "benignant" genetic disease as compared with more severe genetic diseases; however, at least 10% of patients develop malignant complications.

D) Sperm donation (3)

- Sperm donation is the practice by which a man donates his semen to be used specifically to produce a baby. Donation is usually done in sperm banks. Donors may be either anonymous (most are anonymous) or non-anonymous. The national law may restrict the number of children each donor may father (up to 25).
- Potential sperm donors are usually young. The anonymity is controversial and differently regulated in different countries (the identity disclosure is required in some countries but not in others). The consequence of identity disclosure is the shortage of donors, since most donors do not want to be known.
- A limited donor information released to the woman/couple at most includes height, weight, eye, skin and hair colour. Additional information may be eventually given. Usually, sperm donors are protected by law from being responsible for children produced from their donations, and have no rights over the children generated by their sperm.
- Several countries only allow non-anonymous sperm donation. The child may, when grown up, get contact information from the sperm bank about his/her biological father (including health status and

heritable diseases, if known).

- Non-institutional donations include "private" donor by advertising (web sites seek to link private donors and donees). Private donations are usually free - avoiding the costs of a medicalised insemination – and, theoretically, the chances of pregnancy may be higher when fresh rather than frozen semen is used. Against this are the usually higher risks of disease transmission and the risk of a legal dispute regarding access or maintenance. In some countries written agreements between donors and donees in a similar way to institutional donations are recognised.
- The screening of age-dependant heritable diseases, in particular heritable cardiovascular diseases, is impossible. Most sperm banks perform underwent standard testing for infectious diseases, karyotype and test for common genetic diseases such as the recessive cystic fibrosis in the general population (prevalence of healthy carriers 1:30), and genetic conditions common to certain ethnic groups (e.g., sickle cell trait for African Americans).

E) Donor suitability (Sperm banks)

The evaluation of potential donors mostly concentrates on infectious diseases. In the present case (1), the father was screened by a comprehensive personal and family history, physical examination, and by laboratory testing for infectious and transmittable diseases: 1HIV and HIV2, HTLV1 and HTLV2, syphilis, HCMV, HBV and HCV, gonorrhoea and Chlamydia, as well as Tay-Sachs disease.

Physical examination and family history

The personal and family history was carefully evaluated and the father underwent physical examination. Obviously the family history was negative and there were no apparent reasons for family screening. Obviously physical examination, likely including auscultation, was negative. Most sarcomeric HCM do not show extracardiac traits and therefore it is unlikely that physical evaluation may contribute to suspect a HCM.

By instance, the parents of the donor were not investigated after the positive genetic test (non available).

Overall, based on existing rules, the paternal disease had low probability of being recognised before accepting the donor.

F) The phenotype of affected children seems to be more severe than that of the biological father who was diagnosed after the detection of HCM in one of the 2 offspring conceived by the donor's wife. The reasons are not clear/known.

G) Ethical considerations

A genetic disease can be transmitted unwittingly to offspring born by medically assisted procedures with sperm donation. The risk is unpredictable. The present case is likely to appear as a unique case, but the number of medically assisted procedures by sperm donation the absence of a male partner or in the presence of fertility problems is increasing. Another potential, remote and unpredictable risk is the mating of half-siblings. This may depend on the geographic utilisation of the donated sperm, as well as the number of children each donor may father; if the number is high (for example 25), the sperm bank serves local requirements, the genetic disease is highly prevalent in the general population and can be clinically silent, the risk remains low but possible. The HCM case is just an example that pertains the WG field of interest. However, the same risk applies to any other genetic diseases without manifest phenotype at the time of donation. Laws that govern sperm donation should be known by geneticists working in the setting of cardiomyopathies and should probably be matter of unified revision in EU countries.

Question

Should interview about medically assisted procreation and sperm donation be included in genetic counselling for probands with apparently sporadic (de novo) HCM?

References

1. Implications of Hypertrophic Cardiomyopathy Transmitted by Sperm Donation. Maron BJ, Lesser JR, Schiller NB, Harris KM, Brown C, Rehm HL. JAMA. 2009;302:1681-4. Erratum in: JAMA. 2009 Nov 11;302:1972
2. Wirojanan J, Angkustsiri K, Tassone F, Gane LW, Hagerman RJ. A girl with fragile X premutation from sperm donation. *Am J Med Genet A*. 2008;146:888-892.
3. Practice Committee of American Society for Reproductive Medicine; Practice Committee of Society for Assisted Reproductive Technology. 2008 Guidelines for gamete and embryo donation: a Practice Committee report. *Fertil Steril*. 2008;90(5)(5 suppl): S30-S44

The clinical case of the month: *What is your diagnosis?*

Answers will be given in the next newsletter and on the web site

Presented by Michele Pasotti, Fabiana Isabella Gambarin, Alessandra Serio, Luigi Tavazzi*, Eloisa Arbustini

Centre for Inherited Cardiovascular Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia and *GVM Care and Research, Cotignola (Ravenna), Italy.

Misleading phenotype or biased cardiologists?

First clinical evaluation at our centre

A 20-year-old Caucasoid male, a soccer non-competitive athlete was referred to our attention for recent onset exertion dyspnoea and palpitations. He was suspected to be affected by Marfan syndrome (MFS). He was tall (height 190 cm) and weighted 62 Kg. The prior clinical history was negative.

The cardiologic evaluation documented a mild pansystolic murmur consistent with mitral regurgitation. The ECG showed sinus rhythm, HR 67 beats/min, and normal repolarisation pattern (Fig. 1). Two-dimensional echocardiography disclosed mitral valve prolapse with mixomatous degeneration of the mitral leaflets associated with mild mitral regurgitation; the aortic root diameter was at the upper limit of the normal range (aortic root ratio 1.12; z-score 1.62) (fig. 2). Left ventricular dimensions and function were within the normal range. Left atrium and transmitral blood flow were normal. Holter monitoring showed short episodes of paroxystic atrial fibrillation.

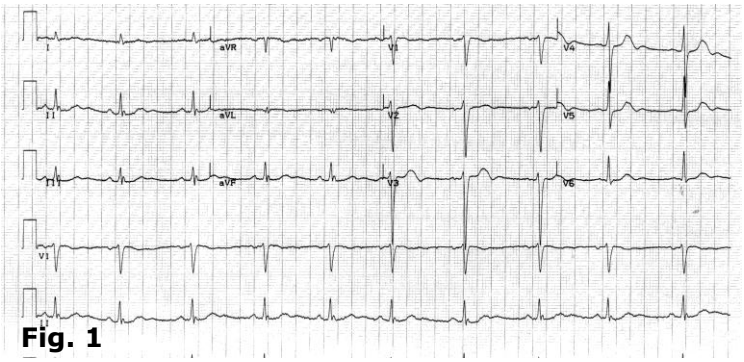

Fig. 1

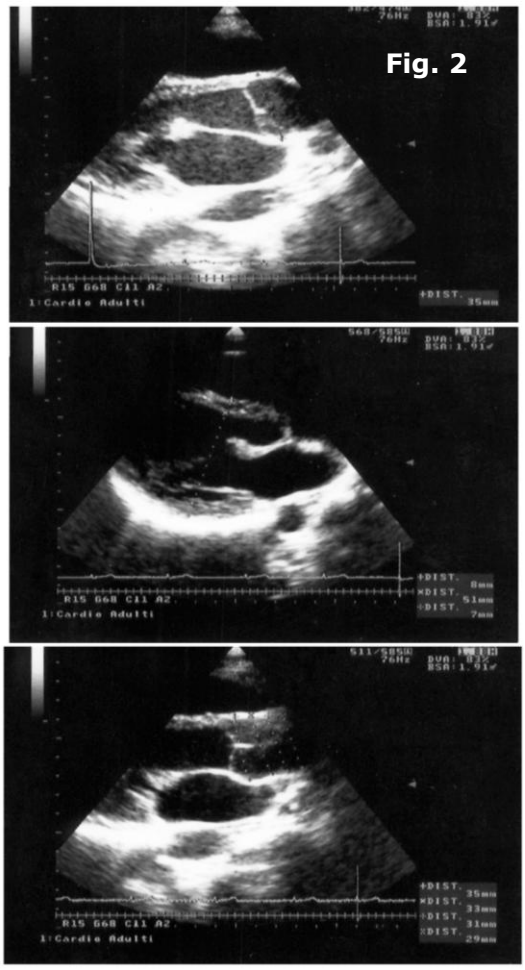

Fig. 2

The orthopaedic evaluation showed:

- pes planus,
- scoliosis <20°.

The patient did not show other skeletal traits suggestive for MFS.

The ophthalmologist evaluation excluded ocular traits.

The lumbosacral MRI documented dural ectasia.

Family history and evaluation (fig. 3)

Mother and maternal lineage

The mother showed mitral valve prolapse with moderate to severe mitral regurgitation, mild left ventricular dilation and preserved left ventricular function. Her skeletal, and ocular phenotype did not show traits suggestive for MFS. The grandmother died suddenly at the age of 62 years; autopsy was not performed. Other maternal relatives did not show cardiovascular abnormalities and none of them had positive history for cardiovascular diseases.

Father and paternal lineage

The father died suddenly at the age of 50 years. He was described as tall and thin and using glasses since young age. No picture was available. From the narrative of the proband, the father had complained, one month before death, non-otherwise specified cardiac "problems". Two paternal uncles (52- and 48-year-old) also died suddenly. Their offsprings were referred to be healthy. One additional uncle was described as healthy as were their offspring. The paternal grandmother also died suddenly at the age of 62 years: she was known to suffer cardiovascular "problems". The paternal relatives who died suddenly did not undergo autopsy.

Sibs

A 22-year-old brother underwent clinical evaluation that documented the absence of extra cardiac traits suggestive for MFS, and ECG and echocardiographic study that showed normal parameters.

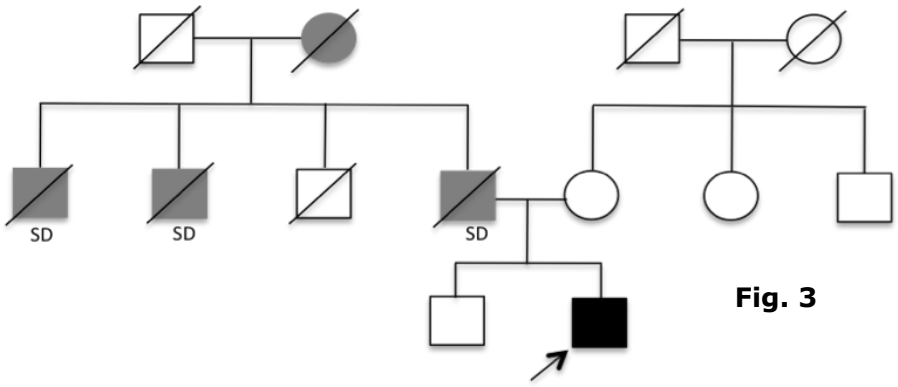

Fig. 3

We excluded Marfan syndrome in the proband on the basis of Ghent criteria (Ref. 1). Independently on the absence of major criteria for MFS, the paternal family history with several sudden deaths, the symptoms, and the short episode of AF deserved further clinical evaluation and monitoring. We suggested medical treatment and proposed beta-blocker. He refused to take drugs and decided to come for further controls on his own scheduling. We did not have further information for about two years, when the patient called our centre and asked for a clinical control.

Second clinical evaluation at our centre 18 months later.

The patient came with clinical reports documenting that one year after our first evaluation, he had a persistent episode of atrial fibrillation that had been successfully controlled with intravenous propafenone. He was not given treatments. Six months after this episode, he suffered a presyncope and was admitted to the local hospital. From the clinical reports, the arterial blood pressure was 95/65 mmHg and oxygen saturation was 98%. ECG showed atrium fibrillation (Fig. 4). Routine biochemical tests were negative. The TEE excluded sources of thromboembolism. He was given anticoagulants and addressed to our centre.

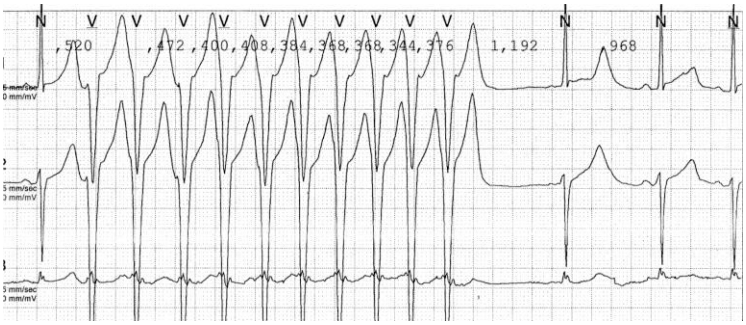

Fig. 4

A TTE study confirmed previous data: in particular, left atrium was normal and there were no sources of thrombolembolism. He underwent successful external electric cardioversion. A few days later, the Holter monitoring documented sinus rhythm (mean heart rate 55 beats/min, range 37-122); isolated PVC (n=30) one episode of non-sustained ventricular tachycardia (fig. 5); isolated and repetitive atrial extrasystoles (maximum 5 beats). He was discharged from the hospital and given beta-blocker therapy (bisoprolol 1.25 mg/day).

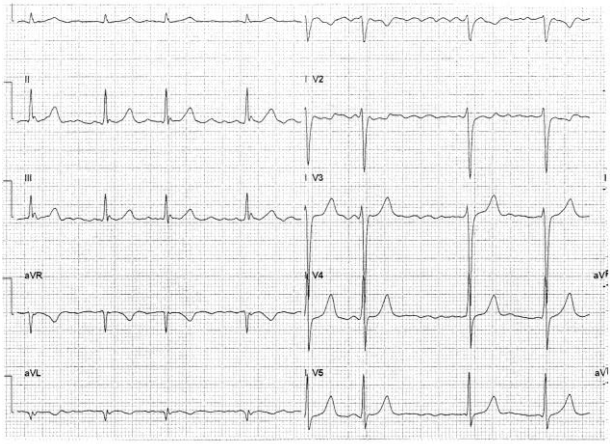

Fig. 5

We repeated an ECG Holter monitoring that confirmed the sinus rhythm interrupted by diurnal and nocturnal short phases of junctional rhythm and documented three episodes of non-sustained ventricular tachycardia (max 10 beats).

Based on these results, we proposed the electrophysiological study that showed:

- no inducible of sustained ventricular arrhythmias;
- mild delay of sub-hissian conduction with regular sinus function;
- absence of AVB;
- induction of reproducible right atrial tachycardia
- induction of typical atrial flutter with fast evolution to atrial fibrillation

A cardiac MR demonstrated increased left ventricular diastolic volume (107 ml/mq) with normal ejection fraction (LVEF = 51%), normal wall thicknesses and absence of late gadolinium enhancement.

Would you suggest further diagnostic investigation?

Do you think that genetic testing for MFS is appropriate?

What is your diagnostic hypothesis, based on the available clinical data?

1. the severe paternal family history of sudden cardiac death
2. the documented short episodes of NSVT in the proband
3. the mild delay of subhissian conduction recorded at the EP study

Due to the difficult clinical orientation, we asked the family to trace the medical records of the father and eventually of other deceased relatives, and to address this material to our attention.

The information about the paternal records and the case resolution will be available next month.

REFERENCES

DePaepe A, Dietz HC, Devereux RB, Hennekem R, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996;62:417-26

Answer for the previous" Clinical case of the month" presented in December

"A case of "bright myocardium" (not all that glitters is gold)"

by Massimiliano Lorenzini, Claudio Rapezzi, University of Bologna and S.Orsola-Malpighi Hospital, Bologna, Italy

Diagnosis, case resolution and treatment

The clinical history of the patient is definitely characterized by "nephrological problems" i.e. recurrent renal colics and renal insufficiency leading to chronic hemodialysis and kidney transplantation. Can we use the term (and the concept of) "*uraemic" cardiomyopathy*" to explain the abnormal cardiologic findings of this case? Indeed, in patients with end-stage renal disease from any cause, left ventricular remodeling frequently occurs, leading to eccentric left ventricular hypertrophy with varying degrees of ventricular dilatation and dysfunction and frequent calcifications of valves' anula and leaflets (especially when secondary hyperparathyroidism coexists). However, this "simple" diagnostic hypothesis would not explain all the key findings of the present case, including the recurrence of renal colics and the "bright" hyper reflecting aspect of ventricular myocardium.

During hospitalization a urine morphological exam documented numerous granular casts, calcium oxalate crystals and amorphous urates. Urinary oxalate was 57 mg/1000 cc in 24 hours (n.v. <34 mg/1000 cc in 24 h).

The hypothesis of *primary hyperoxaluria* was considered and two further examinations were performed: renal biopsy and molecular analysis. The biopsy of the transplanted kidney documented a modest increase in cell count in the glomeruli and mesangial matrix, numerous birefringent oxalate crystals (at polarized light) in the tubular lumen and in the epithelial cells. Extensive diffuse limpho-monocyte interstitial infiltrate, a number of giant cells surrounding the crystals and a discrete amount of fibrosis were also found (Figure 1). The ultrastructural exam showed numerous sizeable crystalline deposits that could morphologically be identified as calcium oxalate crystals in the tubuli and in the interstitium (where a rich inflammatory infiltrate was also present).

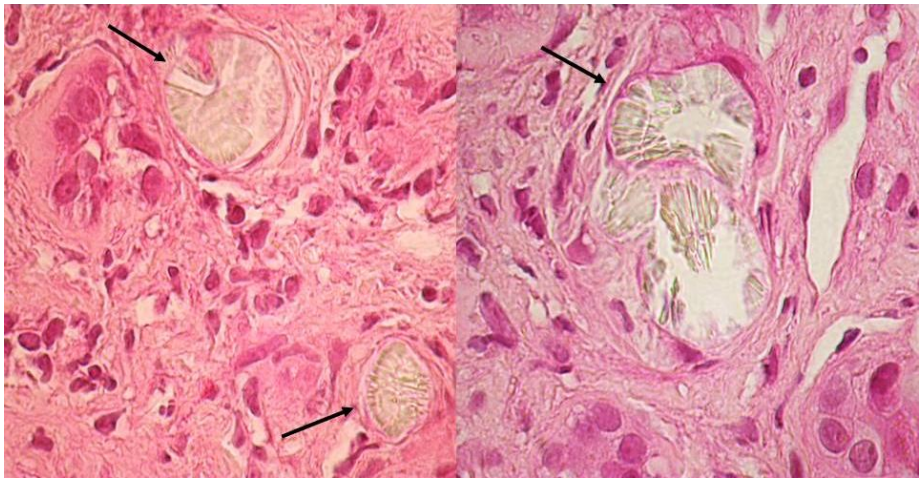

Figure 1: *Histology of the kidney (hematoxilin/eosin; 400 x) showing calcium oxalate crystals in the tubular lumen (arrows).*

To confirm the hypothesis of *primary hyperoxaluria*, molecular analysis of the two encoding genes was peformed [alanine-glyoxylate aminotransferase (AGXT) and glyoxylate reductase/hydroxypyruvate reductase (GRHPR)]. The molecular analysis of the AGXT gene showed the presence of a 508G>>A mutation in the IV exon in heterozygosis that determines an aminoacid substitution in the codon 170 of a glycine with an arginine (G170R) in the encoded protein and a 33insC mutation in the I exon that determines a shift in the reading code of the protein. **The result therefore confirmed the diagnosis of type I primary hyperoxaluria**.

Due to worsening renal function the patient resumed dialysis and received an indication to a combined liver-kidney transplant. The patient successfully underwent the transplant a few months later.

Comment. *Primary Hyperoxaluria* is a rare genetic disease, inherited with an autosomal recessive pattern, characterized by a liver peroxisome enzyme deficiency that causes an abnormal glyoxylate metabolism. It is classified into 2 variants: type I, with a deficiency of alanine-glyoxylate aminotransferase (AGXT) and type II, with a shortage of glyoxylate reductase/hydroxypyruvate reductase (GRHPR). The disease is characterized by a marked hyperoxaluria, calcium oxalate nephrolithiasis, nephrocalcinosis and progressive kidney function reduction. It may also involve the heart through myocardial calcium oxalate deposition, predominantly at intracellular level, determining a storage cardiomyopathy with an echocardiographical appearance of ventricular hypertrophy and a pronounced "granular sparkling" effect. The specialized conduction tissue may also be involved causing electrical conduction blocks. Calcium oxalate may also precipitate in the tunica media of arteries, including coronaries, and may cause non-atheromasic coronary disease in the young .

Since the enzyme deficiency is localized in the hepatic peroxisomes, the only decisive therapy is a liver transplant which represents a "surgical gene therapy".

In this specific case a number of elements are congruent with a diagnosis of primary hyperoxaluria and must elicit the clinical diagnostic suspicion: history of recurrent nephrolitiasis from a young age, renal insufficiency progression, recurrence of nephrolitiasis even after kidney transplantation, and myocardial storage disease with a "granular sparkling", bright appearance on echocardiogram.

References

1. Hoppe B, Beck BB, Milliner DS. The primary hyperoxalurias. Kidney Int. 2009;75:1264-71.
2. Bobrowski AE, Langman CB. The primary hyperoxalurias. Semin Nephrol. 2008;28:152-62.
3. Cochat P, Liutkus A, Fargue S, Basmaison O, Ranchin B, Rolland MO. Primary hyperoxaluria type 1: still challenging! Pediatr Nephrol. 2006;21:1075-81.
4. Meyburg J, Hoffmann GF. Liver transplantation for inborn errors of metabolism. Transplantation. 2005;80 (1 Suppl) :S135-7.
5. Pais VM Jr, Assimos DG. Pitfalls in the management of patients with primary hyperoxaluria: a urologist's perspective. Urol Res. 2005;33:390-3.
6. Rumsby G. An overview of the role of genotyping in the diagnosis of the primary hyperoxalurias. Urol Res. 2005;33:318-20.
7. Danpure CJ. Molecular etiology of primary hyperoxaluria type 1: new directions for treatment. Am J Nephrol. 2005;25:303-10

List of recently published papers in the field of our WG recommended for further reading:

1. Cardiac infections: focus on molecular diagnosis. Calabrese F, Carturan E, Thiene G. Cardiovasc Pathol. 2010 Jan 11 epub ahead of print

2. Contemporary insights and strategies for risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. Maron BJ. Circulation. 2010 Jan 26;121(3):445-56.

3. Heart transplantation in women with dilated cardiomyopathy. Regitz-Zagrosek V, Petrov G, Lehmkuhl E, Smits JM, Babitsch B, Brunhuber C, Jurmann B, Stein J, Schubert C, Merz NB, Lehmkuhl HB, Hetzer R. Transplantation. 2010 Jan 27;89(2):236-44.

4. Myozap, a Novel Intercalated Disc Protein, Activates Serum Response Factor-Dependent Signaling and Is Required to Maintain Cardiac Function In Vivo. Seeger TS, Frank D, Rohr C, Will R, Just S, Grund C, Lyon R, Lüdde M, Koegl M, Sheikh F, Rottbauer W, Franke WW, Katus HA, Olson EN, Frey N. Circ Res. 2010 Jan 21. Epub ahead of print

5. Measurement of trabeculated left ventricular mass using cardiac magnetic resonance imaging in the diagnosis of left ventricular non-compaction. Jacquier A, Thuny F, Jop B, Giorgi R, Cohen F, Gaubert JY, Vidal V, Bartoli JM, Habib G, Moulin G. Eur Heart J. 2010 Jan 19. Epub ahead of print

6. Prevalence and natural history of heart disease in adults with primary mitochondrial respiratory chain disease. Limongelli G, Tome-Esteban M, Dejthevaporn C, Rahman S, Hanna MG, Elliott PM. Eur J Heart Fail. 2010 Feb;12(2):114-21.

7. Severe familial left ventricular noncompaction cardiomyopathy due to a novel troponin T (TNNT2) mutation. Luedde M, Ehlermann P, Weichenhan D, Will R, Zeller R, Rupp S, Müller A, Steen H, Ivandic BT, Ulmer HE, Kern M, Katus HA, Frey N. Cardiovasc Res. 2010 Jan 18. Epub ahead of print