Cancer Prone Disease Section
Review

Alport syndrome and diffuse leiomyomatosis

Lobna Ayadi, Karima Abbes, Saloua Makni, Mahmoud Kharrat, Rim Kallel, Najmeddine Affes, Mohamed Ben Hmida, Jamil Hachicha, Mohamed Issam Beyrouti, Tahya Sellami Boudawara

Department of Pathology, Habib Bourguiba University Hospital, SFAX, Tunisia (LA, KA, SM, RK, TSB); Department of nephrology, Hedi Chaker University Hospital, SFAX, Tunisia (MK, MBH, JH); Department of surgery, Habib Bourguiba University Hospital, SFAX, Tunisia (NA, MIB)

Identity

Note

Alport Syndrome (AS) is a rare hereditary glomerular nephropathy, its incidence is approximatively 1/5000 individuals.

Its association with leiomyomatosis is estimated at 5% of the cases. Leiomyomatosis tends to affect young boys (mean age: 6 years) and women at a mean age of 40 years. In contrast to the renal lesions which are less severe among women, the leiomyomatosis is as severe in women as in men.

Inheritance

- X-linked inheritance:

The primary mode of inheritance of AS is X-linked dominant (85% of the patients): Indeed, mutations in COL4A5 collagen gene are responsible for the more common X-linked dominant form of the disease, characterized by its allelic heterogeneity (more than 300 different mutations of the COL4A5 gene). This particular type of transmission causes severe disease in the male patient and a varied presentation of the syndrome in females. The broad range of phenotypes for women is caused by random inactivation of one X chromosome causing two populations of cells within organ systems (lyonisation).

- Autosomal inheritance:

Approximatively 15% of all cases of Alport syndrome are due to autosomal inheritance. Autosomal recessive inheritance has been cited as a rare occurrence, due to mutations of the COL4A3 and COL4A4 genes coding for the collagen IV alpha 3 and alpha 4 chains, both located on the long arm of chromosome 2.

The autosomal-dominant form of AS is questionable and should be considered if male-to-male inheritance is discovered.

Clinics

Note

AS is a rare hereditary glomerular nephropathy, its incidence is estimated at 1 in 5000 individuals. It was first described by Alport in 1927. AS is a progressive hematuric nephropathy with progression to renal failure, due to changes in the collagen IV of the glomerular basement membrane. The hematuria can occur sporadically, or associated with a proteinuria, and even with a nephrotic syndrome or a chronic renal insufficiency. In addition to the renal lesions, a sensorineural loss is frequently reported; it is bilateral and never congenital. The ocular lesions with anterior lenticonus, maculopathy and congenital cataract are specific and are found in the third of the cases. The mode of inheritance of AS was discussed a long time; in approximately 85% of the patients, AS is X-linked dominant, characterized by its allelic heterogeneity.

AS is exceptionally revealed by a leiomyomatosis, which can interest the oesophagus, the tracheo-bronchial tree or the genital tract in women. In the series of Jet and al. this association is estimated at 5% of the cases. Other studies report that AS can be present at more than 72% of the children with oesophageal leiomyomatosis.

The leiomyomatosis is a benign lesion, which consists of a tumor-like hypertrophy of the smooth muscle. Leiomyomatosis tends to affect young boys (mean age: 6 years) and women (mean age: 40 years). In contrast to the renal lesions which are less severe among women, the leiomyomatosis is as severe in women as in

men. This disease affects preferentially the lower third of oesophagus, and may extend down into the cardia. The oesophageal lesions can be diffuse, extensive or multinodular. Clinical symptoms are attributed to signs of compression of the oesophagus or neighbouring organs. They commonly include progressive dysphagia, vomiting or dyspepsia; less frequently, retrosternal pains, dyspnea, cough or weight loss. The Barium contrast study is the best diagnosis tool revealing a widened upper oesophagus and a smooth tapered narrowing of the distal oesophagus with reduced oesophageal motility; such findings often lead to the misdiagnosis of achalasia in up to 50% of patients. The leiomyomatosis is histologically defined by a proliferation of interlacing whorls of smooth muscle cells without evidence of mitotic figures or atypia, and staining with smooth muscle actin (SMA).

Phenotype and clinics

Kidney: The hematuria (99%) is the earliest clinical sign with variable severity. It can occur sporadically, or associated with a proteinuria, and even with a nephrotic syndrome or a chronic renal insufficiency. Systemic hypertension will result with continued deterioration of the renal system. Renal lesions are less severe among women.
Ear: Hearing loss (82.5%) is bilateral and never congenital. Auditory manifestations appear to parallel the severity of renal involvement and may be coincident with ocular signs. Females with Alport syndrome are less severly affected and the deficit is usually non-progressive.
Eye: The ocular changes (44%) are specific: anterior lenticonus, maculopathy and congenital cataract. Males have equal or greater ocular involvement compared to females.
Leiomyomatosis: 5%; **Oesophagus**: the most frequent is distal oesophagus and cardia;
Genital: periclitoridian region, vulvar, hypertrophy of minor and major labia, perineal lesions; **Respiratory**: Tracheo bronchial localisation is less common but may be lethal due to bronchospasm.

Neoplastic risk

No neoplastic risk is associated to Alport syndrome.

Treatment

No cure is available at this time.
Management of Alport syndrome:
Genetic counselling: Appropriate genetic counceling is essential for the management of Alport syndrome. Carrier identification is important for the proband's family especially if the urinalysis findings are inconsistent. Molecular genetics can be used to determine the amino acid sequence of the genetic lesion. This is important since 85% of X-linked disease is due to a point mutation.
Complications secondary to the renal disease are minimized by controlling hypertension and protein intake. Current treatment end-stage renal disease requires dialysis and/or renal transplantation. Treatment of the hearing deficiency includes
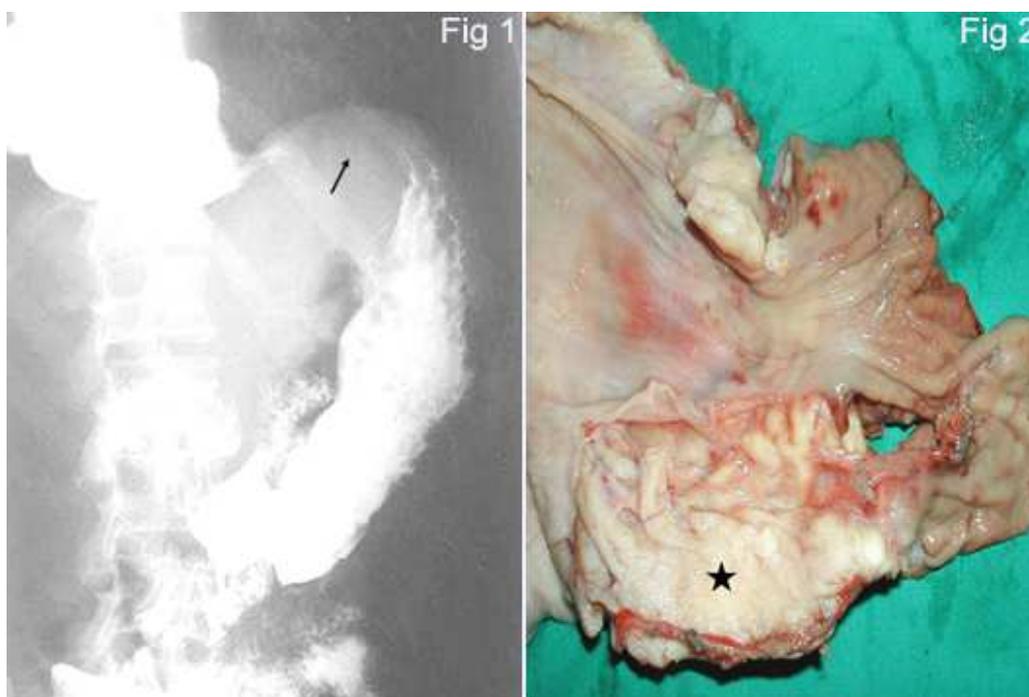

Figure 1: Barium contrast study: a filiform luminal narrowing of the distal oesophagus (→) and a widened upper oesophagus.
Figure 2: Operative photograph showing massive distal leiomyomatosis with markedly thickened oesophageal wall (*).
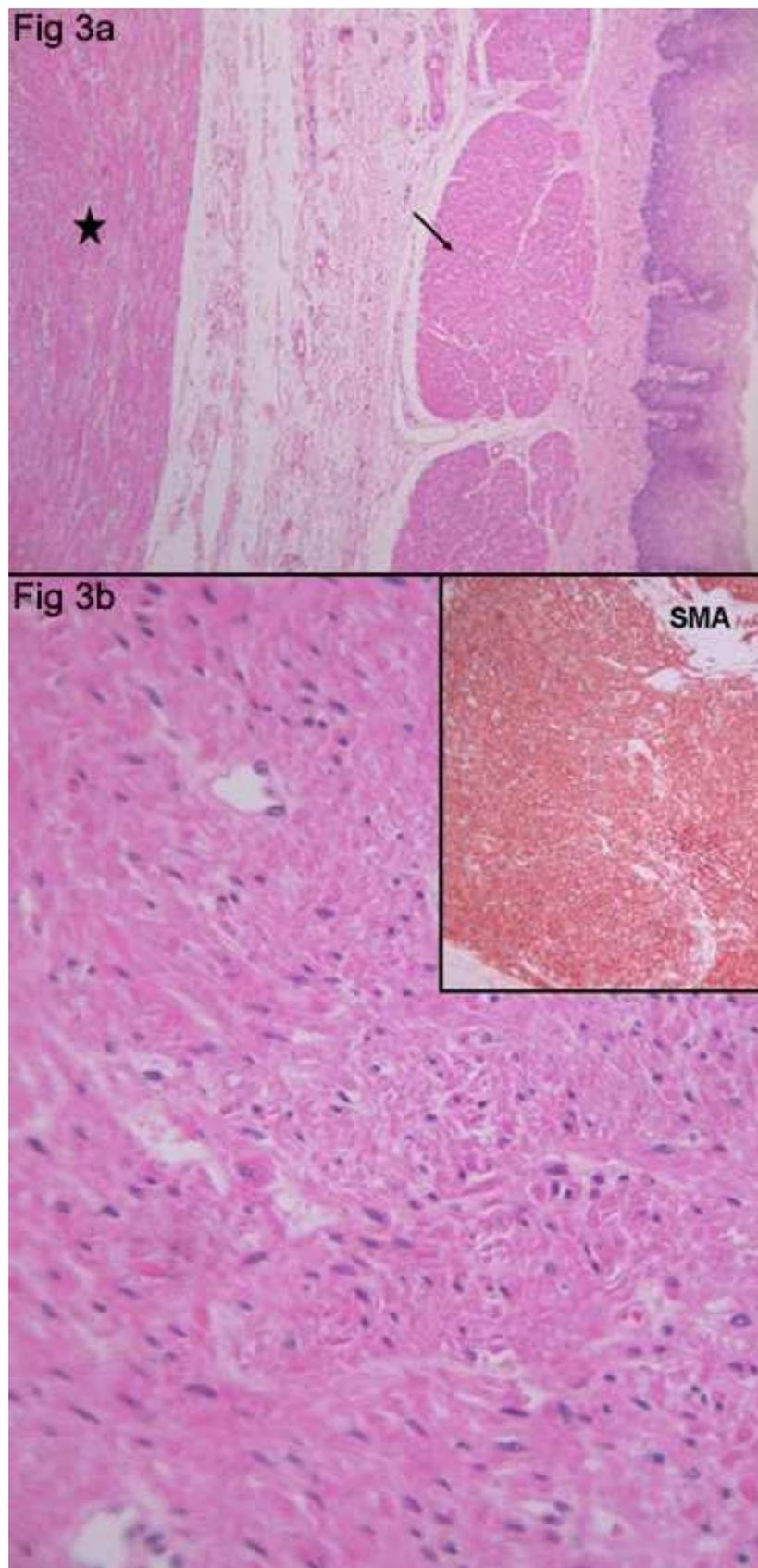
Figure 3a: Nodular muscular overgrowth (*); note hypertrophy of the muscularis mucosa (→) (HEx 200).
Figure 3b: Proliferation of interlacing whorls of smooth muscle cells without evidence of mitotic figures or atypia (HEx400). In set: positive immunostaining with smooth muscle actin (SMA) (x 400).

management of the possible ototoxicity side effect when medications for renal problems are used. Reduced vision secondary to lenticular changes are treated with topical mydriatics or cataract extraction and the application of lenses. Surgery is required for associated leiomyomatosis.

Evolution

In the X-linked form of AS, nephropathy always leads to the final renal insufficiency in men.

Prognosis

Alport syndrome: progression to renal failure.
Leiomyomatosis: recurrence (Postoperative follow-up is required in patients receiving surgery particularly in the pediatric population; long term surveillance for recurrence of disease is necessary).

Other findings

Note
There is a phenotype-genotype correlation.
Cases of Alport syndrome associated with diffuse leiomyomatosis are caused by some COL4A5 deletion mutations extending into COL4A6. The extent of the deletion into COL4A6 is limited to the alternative exons 1 and 1', intron 1, exon 2, and part of the very large intron 2. If the deletion extends into exon 3, then diffuse leiomyomatosis is not observed.

Genes involved and proteins

Note
Mutations in the collagen alpha 5(IV) chain gene COL4A5 extending into COL4A6. More than 300 different mutations of the COL4A5 gene in the X-linked Alport syndrome. Type IV collagen is a family of six proteins, the a 1(IV)- a 6(IV) chains, each encoded by its own gene (COL4A1-COL4A6). The six type IV collagen genes are distributed in pairs on three different chromosomes: COL4A1-COL4A2 on chromosome 13, COL4A3-COL4A4 on chromosome 2, and COL4A5-COL4A6 on the X chromosome. The members of each pair are oriented in a 5'-5' manner, with the transcriptional initiation sites separated by DNA sequences containing regulatory elements.
The type IV collagen a chains possess a noncollagenous domain (NC1) at the carboxyterminal end, a central collagenous domain consisting of Gly-X-Y repeats, and a short amino-terminal non-collagenous (7S) domain. Type IV collagen a chains form trimers through associations between their carboxyterminal NC1 domains, which initiate folding of the collagenous domains into triple helices. Variable residues within the NC1 domains appear to indicate which chains can interact with each other.
The type IV collagen trimers associate with each other via carboxy- and amino-terminal interactions to create basement membrane network. Evidence from a variety of sources indicates the existence of at least three type

IV collagen hetero-trimers in mammalian basement membranes, a1(IV)2 a2(IV), a3(IV)- a4(IV)- a5(IV) and a5(IV)2 a6(IV). The a1(IV)2, a2(IV) hetero-trimer is found in all basement membranes, although it is a relatively minor component of glomerular basement membrane (GBM), in which the a3(IV) a4(IV) - a5(IV) heterotrimer predominates. The a3(IV)- a4(IV)- a5(IV) hetero-trimer also occurs in the Bowman's capsule and the basement membranes of distal and collecting tubules. The a5(IV)2a6(IV) hetero-trimer is present in the Bowman's capsule and distal and collecting tubule basement membranes, but not present in GBM. The epidermal basement membrane (EBM) contains a1(IV)2- a2(IV) and a5(IV)2 a6(IV) hetero-trimers, but not the a3(IV)- a4(IV)- a5(IV) hetero-trimers.
These requirements have important consequences for patients with AS, which can arise from mutations in any of a3(IV), a4(IV) or a5(IV) chains. First, COL4A5 mutations that result in failure to synthesize an a5(IV) chain (deletions) or synthesis of a truncated or nonsensical chain (frameshift, premature stop codon, etc.), prevent the formation of trimers containing the a3(IV) and a4(IV) chains.
The result is that none of the three chains appears in basement membrane. Second, missense mutations in COL4A5, in particular those that result in replacement of a glycine residue in the collagenous domain of the a5(IV) chain by another amino acid, allow the formation of abnormally folded trimers that are highly susceptible to extracellular degradation before being incorporated into basement membranes. Again, the consequence of the mutation in the a5(IV)chain is the elimination of all three chains from basement membranes. In some instances, a missense mutation may allow formation of an abnormal network that is deposited in basement membranes.
Mutations in the a3(IV) and a4(IV) chains can have similar effects, particularly in basement membranes such as GBM in which the a6(IV) chain is not expressed, so that a5(IV) chains can form hetero-trimers with only the a3(IV) and a4(IV) chains. In the Bowman's capsule, distal and collecting tubules basement membranes, and epidermal basement membranes, the a5(IV) chain can be expressed even in the absence of the a3(IV) or a4(IV) chains, because these basement membranes express the a6(IV) chain, with which the a5(IV) chain can form trimers.

DNA/RNA

Note
X-linked Alport syndrome is caused by mutations in the collagen alpha 5(IV) chain gene COL4A5.
Mutations in COL4A3 and COL4A5, which are linked head-to-head on chromosome 2, are responsible for the autosomal forms of the disease.
COL4A6 is located on the X chromosome head-to-head with COL4A5 and some COL4A5 deletion mutations that cause Alport syndrome extend into COL4A6. Thus the 5' ends of both genes are affected. Cases of Alport

syndrome associated with diffuse leiomyomatosis also fall into this category, but the extent of the deletion into COL4A6 is limited to the alternative exons 1 and 1', intron 1, exon 2, and part of the very large intron 2. Interestingly, if the deletion extends into exon 3, then diffuse leiomyomatosis is not observed.

A COL4A6 transcript including exon 4, but not exon 3, was found in tumor samples of leiomyomatosis, raising the possibility of the involvement of a truncated alpha6 chain of type IV collagen in the benign tumorous process.

Alport syndrome associated with leiomyomatosis is transmitted as X-linked dominant traits. Women with diffuse leiomyomatosis transmit Alport syndrome. An antenatal diagnosis can be proposed for such patients.

Genetic Hypothesis/histogenesis:

It was postulated that the most restricted deletion may allow production of a truncated a6 chain in the smooth muscle, which might be capable of aberrant signalling and leads to benign proliferation.

Another hypothesis stipulates that the presence of a gene located on intron 2 of COL4A6 which is transformed into a dominating promoter of the smooth muscle overgrowth.

Other studies, postulate that the loss of the 4.2-kb region, containing the proximal promoters of COL4A5-COL4A6 genes, causes misregulation of neighbouring genes, contributing to the smooth muscular overgrowth.

References

García-Torres R, Orozco L. Alport-leiomyomatosis syndrome: an update. Am J Kidney Dis. 1993 Nov;22(5):641-8

Dahan K, Heidet L, Zhou J, Mettler G, Leppig KA, Proesmans W, David A, Roussel B, Mongeau JG, Gould JM. Smooth muscle tumors associated with X-linked Alport syndrome: carrier detection in females. Kidney Int. 1995 Dec;48(6):1900-6

Antignac C, Heidet L. Mutations in Alport syndrome associated with diffuse esophageal leiomyomatosis. Contrib Nephrol. 1996;117:172-82

Heidet L, Cai Y, Sado Y, Ninomiya Y, Thorner P, Guicharnaud L, Boye E, Chauvet V, Solal LC, Beziau A, Torres RG, Antignac C, Gubler MC. Diffuse leiomyomatosis associated with X-linked Alport syndrome: extracellular matrix study using immunohistochemistry and in situ hybridization. Lab Invest. 1997 Feb;76(2):233-43

Federici S, Ceccarelli PL, Bernardi F, Tassinari D, Zanetti G, Tani G, Dòmini R. Esophageal leiomyomatosis in children: report of a case and review of the literature. Eur J Pediatr Surg. 1998 Dec;8(6):358-63

Miner JH. Alport syndrome with diffuse leiomyomatosis. When and when not? Am J Pathol. 1999 Jun;154(6):1633-5

Jais JP, Knebelmann B, Giatras I, De Marchi M, Rizzoni G, Renieri A, Weber M, Gross O, Netzer KO, Flinter F, Pirson Y, Verellen C, Wieslander J, Persson U, Tryggvason K, Martin P, Hertz JM, Schröder C, Sanak M, Krejcova S, Carvalho MF, Saus J, Antignac C, Smeets H, Gubler MC. X-linked Alport syndrome: natural history in 195 families and genotype-phenotype correlations in males. J Am Soc Nephrol. 2000 Apr;11(4):649-57

Levy M, Gubler MC, Feingold J. [Contribution of genetics to knowledge and management of hereditary kidney diseases progressing to renal failure]. Arch Pediatr. 2001 Oct;8(10):1086-98

Calabrese C, Fabbri A, Fusaroli P, Di Gaetano P, Miglioli M, Di Febo G. Diffuse esophageal leiomyomatosis: case report and review. Gastrointest Endosc. 2002 Apr;55(4):590-3

Thielen BK, Barker DF, Nelson RD, Zhou J, Kren SM, Segal Y. Deletion mapping in Alport syndrome and Alport syndrome-diffuse leiomyomatosis reveals potential mechanisms of visceral smooth muscle overgrowth. Hum Mutat. 2003 Nov;22(5):419

Lee LS, Nance M, Kaiser LR, Kucharczuk JC. Familial massive leiomyoma with esophageal leiomyomatosis: an unusual presentation in a father and his 2 daughters. J Pediatr Surg. 2005 May;40(5):e29-32

Maziers N, Dahan K, Pirson Y. [From Alport syndrome to benign familial hematuria: clinical and genetic aspect]. Nephrol Ther. 2005 May;1(2):90-100

Gubler MC. Diagnosis of Alport syndrome without biopsy? Pediatr Nephrol. 2007 May;22(5):621-5

Gubler MC, Heidet L, Antignac C. [Alport syndrome or progressive hereditary nephritis with hearing loss]. Nephrol Ther. 2007 Jun;3(3):113-20