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Early Progression of Xanthogranulomatous Pyelonephritis in Children Might Be Dependent on Vimentin Expression

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 7
Final Diagnosis: Xanthogranulomatous pyelonephritis
Symptoms: Leucocyturia
Medication: —
Clinical Procedure: Nephrectomy
Specialty: Nephrology

Objective: Unusual clinical course





Background: Xanthogranulomatous pyelonephritis (XP) is an extremely rare, severe, atypical form of chronic renal parenchymal inflammation accompanied by hydronephrosis and/or urolithiasis. The pathomechanism of XP is not yet fully understood. Microscopically, XP is indicated by the presence of multinucleated giant cells and lipid-laden macrophages, as well as inflammatory infiltration and intensive renal fibrosis. The lipid accumulation in kidney parenchyma may be secondary to the altered flow of low-density lipoprotein (LDL)-derived cholesterol particles inside the affected cells. Physiologically, the process of LDL-derived cholesterol transport from lysosomes to the sites of its esterification is dependent on vimentin, which is a molecule comprising the cytoskeleton in mesenchymal cells.

Case Report: A 7-year old girl was hospitalized because of the finding of unexplained kidney lesions on an abdominal ultrasound examination (an enlarged and deformed collecting system of the right kidney with hyperechogenic, solid, staghorn lesions in the calyces). Three months earlier, the patient had experienced recurrent urinary tract infection. Based on the subsequent laboratory and imaging diagnostics, the final diagnosis of XP was established and the girl was qualified for right-sided nephrectomy. Microscopic examination revealed numerous foci of granuloma formations with no evident exponents of dysplastic or neoplastic abnormalities. Significant CD68-positive cell infiltrations and scattered foam cells arranging the numerous foci of granuloma inflammation were noticed. Renal parenchyma, adjacent to granuloma lesions, presented a vimentin expression.

Conclusions: Vimentin expression in XP may confirm a focal character of chronic granuloma formation and may suggest the complexity of XP pathogenesis involving not only macrophage and fibroblast activation but also local lipid regulation and fibrosis.

MeSH Keywords: Immunohistochemistry • Nephritis, Interstitial • Pyelonephritis, Xanthogranulomatous

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Background

Xanthogranulomatous pyelonephritis (XP) is an extremely rare, severe, atypical form of chronic renal parenchymal inflammation accompanied by hydronephrosis and/or urolithiasis [1]. It accounts for approximately 6–10/1,000 surgically proven cases of chronic pyelonephritis. It is more common in women, with a peak incidence in the sixth and seventh decades, and usually follows chronic diseases such as diabetes or leukemia. Its manifestations mimic those of neoplastic and other inflammatory renal parenchymal diseases and, consequently, it is often misdiagnosed clinically [2,3]. The clinical manifestation of XP is not specific. Patients often appear chronically ill. The most common symptoms include fever, chills, anorexia-related weight loss, and flank lumbar pain that is usually dull and persistent.

In children, XP is diagnosed sporadically. Only single case reports have been described so far, and limited cohort studies (involving up to 30 children) have been designed and performed. In the majority of cases, however, XP occurs in girls [4,5]. Nephrectomy is a treatment of choice in all cases, and if done, the future prognosis for the affected child is excellent.

The pathomechanism of XP is not yet fully understood [3]. Occasionally, it may mimic tuberculosis, sarcoidosis, or Wegener granulomatosis [2,6–8]. In most cases, an ineffectively treated pyelonephritis (secondary to calculus or non-calculus urinary obstruction), chronic renal ischemia, lipid metabolism disorders, and, finally, an altered immune response are believed to destroy renal parenchyma and develop areas with the distinctly yellow tinge, which gave the name of the disease [9,10]. A developing failure of one kidney leads to the compensatory overgrowth of the opposite kidney. Such a hypertrophy is regarded as a late XP symptom.

Microscopically, XP is indicated by the presence of multinucleated giant cells and lipid-laden macrophages, as well as inflammatory infiltration, intensive fibrosis, and glomerular sclerosis [11]. The lipid accumulation in kidney parenchyma is one of the most mysterious symptoms. Most likely, it is secondary to the altered flow of low-density lipoprotein (LDL)-derived cholesterol particles inside the affected cells. Physiologically, the process of LDL-derived cholesterol transport from lysosomes to the sites of its esterification is dependent on vimentin, which is a molecule comprising the skeleton in mesenchymal cells [12]. Moreover, the process of kidney fibrosis is initiated by epithelial-mesenchymal transition which can be demonstrated by vimentin presence in the switched cells [13].

Is it then possible that vimentin is a key factor provoking lipid accumulation and renal fibrosis in XP patients? An attempt to answer this question was made by the careful study of the

case history of a 7-year-old girl who was diagnosed with an early stage of XP.

Case Report

A 7-year-old girl was admitted to the Department of Pediatric Nephrology, Poznan University of Medical Sciences because of the finding of unexplained kidney lesions on abdominal ultrasound examination (Figure 1). Three months earlier, the patient had experienced recurrent urinary tract infection (treated with oral antibiotics in the following order: cefuroxime, amoxicillin with clavulanic acid, and sulfamethoxazole with trimethoprim). An abdominal ultrasound performed in an outpatient setting revealed an enlarged and deformed collecting system of the right kidney with hyperechogenic, solid, staghorn lesions in the calyces. The patient and family medical history were negative.

On admission, the girl did not report any pain. On physical examination the following was found: regular heart rate 97 beats/minute, blood pressure 117/61 mm Hg, symmetrical vesicular murmur above the lung fields, soft abdomen, slightly tender to deep palpation in the hypogastrium region, and bilaterally negative costa-vertebral angle tenderness.

In laboratory tests, a complete peripheral blood count, inflammatory markers, activated partial thromboplastin time and prothrombin time, international normalized ratio (INR), concentrations of fibrinogen, total protein, glucose, sodium, potassium, chloride, calcium, magnesium and phosphates, liver enzymes, C3 and C4 complement components, G, M, A immunoglobulins, and antistreptolysin titer were all normal. GFR by the Schwartz formula was 121 mL/min/1.73 m². The QuantiFERON test excluded *Mycobacterium tuberculosis* infection. The urinalysis revealed leukocyturia and erythrocyturia. Proteinuria was absent. Daily excretion of uric acid, calcium, magnesium, phosphates, citrates, and oxalates were within the reference ranges. A significant quantity of *Escherichia coli* (100,000 cfu/mL) was cultured in her urine. The patient was administered an intravenous antibiotic, in accordance with the antibiogram (cefuroxime).

During hospitalization, an abdominal CT scan without a contrast agent was performed. It revealed an enlarged and deformed calyceal system and significantly reduced thickness of the right kidney parenchyma. In the right renal pelvis and the calyceal system, a heterogeneous masses were found with the density of 15–30 Hounsfield units (HU), as well as the presence of six deposits or calcifications with the density of 300–1200 HU, of the size 2–7 mm. The location, size, and structure of the left kidney were normal (Figure 2). Due to the ambiguity of CT images, the diagnostics was expanded to abdominal MRI. It has revealed the right kidney of the length of 78 mm was in a typical location. Within the enlarged and deformed

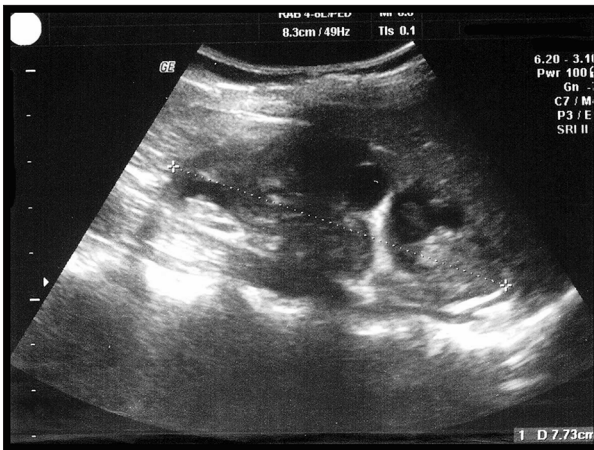


Figure 1. Abdominal ultrasound scan shows enlarged and deformed collecting system of the right kidney with hyperechogenic, solid, staghorn lesions in the calyces.



Figure 2. Abdominal CT scan without contrast agent reveals enlarged and deformed calyceal system and significantly reduced thickness of the right kidney parenchyma. In the right renal pelvis and the calyceal system, heterogeneous masses are found (with the density of 15–30 HU), and the presence of six deposits or calcifications (with the density of 300–1,200 HU) of the size 2–7 mm.

collecting system of the right kidney, numerous, well-delimited, circular, and polycyclic lesions were found, which mainly fill the middle and lower calyces (with intermediate signal intensity in T1-weighted images and with low intensity in T2-weighted images), without contrast intensification in the sequences after the administration of a contrast medium. The right renal parenchyma narrowed to 1.5–5.0 mm, with diffusion restriction (possibly due to cellular-lymphocyte infiltrations). The left kidney was demonstrated as normal (length

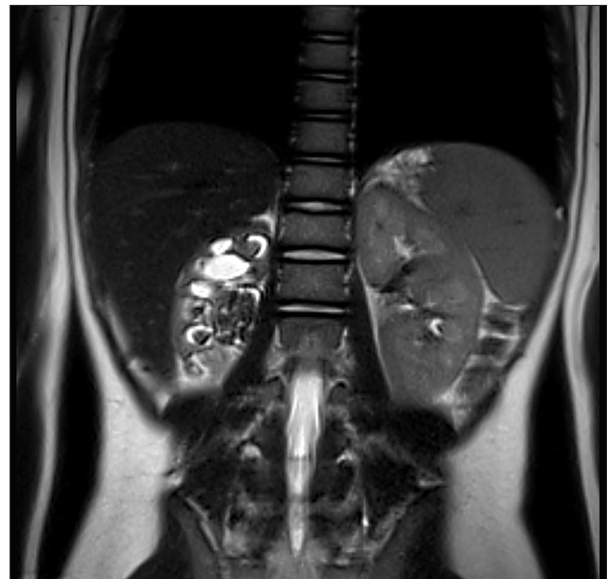


Figure 3. Abdominal MRI reveals the right kidney of the length of 78 mm in a typical location. Within the enlarged and deformed collecting system of the right kidney, numerous well-delimited, circular and polycyclic lesions were found, which mainly fill the middle and lower calyces (with intermediate signal intensity in T1-weighted images and with low intensity in T2-weighted images), without contrast intensification in the sequences after the administration of a contrast medium.

of 96 mm, with a filled collecting system, without narrowing of the parenchyma, Figure 3).

In renal scintigraphy with the use of a radioactive tracer (technetium isotope), the contribution of the right kidney to the total renal function was estimated as 11%. Due to the persisting leukocyturia revealed in the follow-up urinalysis and in view of the fact that a mixed flora was cultured from another urine culture, the antibiotic therapy was modified (ciprofloxacin was administered). Subsequently, sulfamethoxazole and trimethoprim were introduced in an outpatient setting. After one month, a single, oval-shaped lymph node up to 12 mm long was revealed in the right lumbar region by the ultrasound examination, and a trace of interloop fluid in the peritoneal cavity, with the thickness of 3 mm; right kidney was described with no corticomedullary differentiation, with a deformed collecting system, renal parenchyma narrowed to 2–5 mm.

Based on the laboratory and imaging diagnostics, the final diagnosis of XP was established.

After urological consultation, the girl was qualified for right-sided nephrectomy under general anesthesia. During the operation, yellow-colored masses were found within the renal pelvis of right kidney (Figure 4).

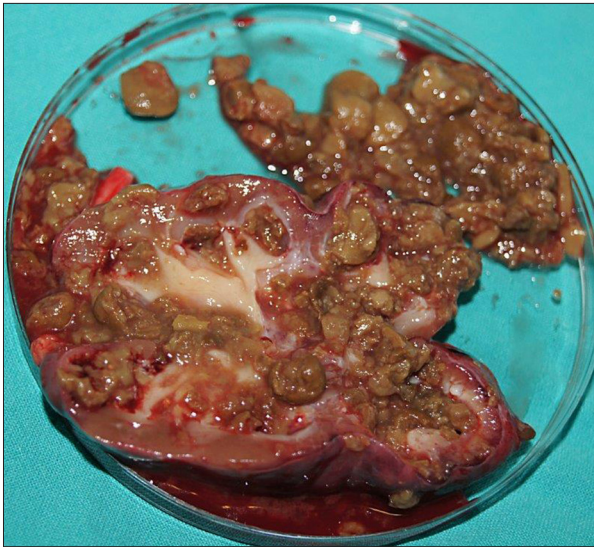


Figure 4. The longitudinal section of the right kidney involved by xanthogranulomatous pyelonephritis. The renal parenchyma expresses the yellowish tinge with the pale area of diffuse scarring.

A microscopic examination of the collected material (right kidney with the proximal portion of the ureter) showed renal texture with partly impaired architectonics, with a focal extension of regressive lesions (atrophy, thyroidization, and fibrosis) and chronic, focal inflammatory process with the formation of lymphoid follicles. Approximately 50% of the renal glomeruli showed hyalinization. The established histological diagnosis was as follows: chronic pyelonephritis.

One month after the surgery, the patient was admitted to the hospital for control laboratory and imaging follow-up. On physical examination, no significant deviations were reported (proper healing of the postoperative wound). Markers of the left renal function and urine analysis were normal in the laboratory studies. The abdominal ultrasound showed the condition after the removal of the right kidney, the site of organ removal was filled with intestinal loops. The left kidney without urine retention and without deposits, with normal parenchymal thickness and structure. The girl was discharged home in good condition.

Histology

The explanted kidney was cut longitudinally in two pieces. One half was placed in Bouin solution for approximately 24 hours, embedded in paraffin and cut at 4 μ m sections. The sections were subsequently deparaffinized and incubated overnight in a humidified chamber with the following specific antibodies: anti-vimentin (Dako, M7020, clone Vim 3B4, diluted 1: 25), anti-CD68 (Dako, M0814, clone KP1, diluted 1: 50) and anti-Ki-67 (Dako, M0814, clone MIB-1, diluted 1: 75).

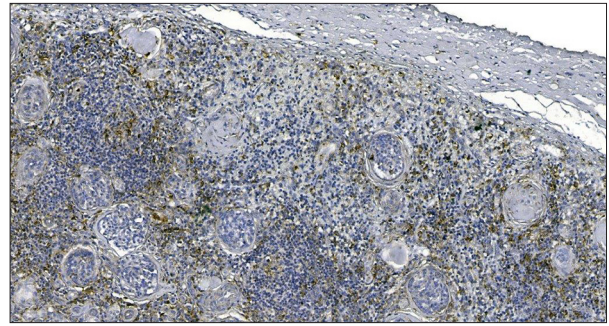


Figure 5. The immunohistochemical expression of CD 68 positive macrophages within renal parenchyma of xanthogranulomatous pyelonephritis.

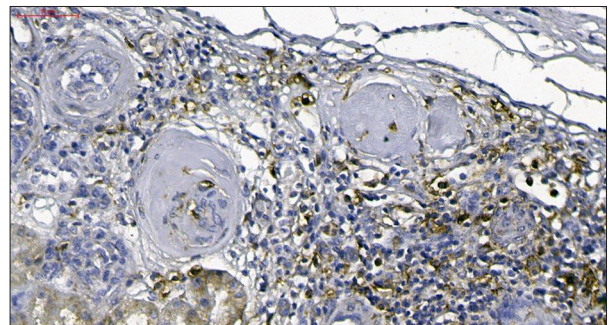


Figure 6. The immunoreactivity for CD 68 within renal parenchyma intensity focused around the glomerular fibrosis.

Immunohistochemical reactions were performed by employing Dako EnVision Detection System, Peroxidase/DAB+, Rabbit/Mouse (K5007). Finally, the slides were counterstained with hematoxylin. Negative controls were performed with the use of normal mouse IgG at the same concentrations as the primary antibodies (Dako, X0931).

Grossly, the renal parenchyma has performed a yellowish tinge with areas of diffuse scarring (Figure 4). Microscopic examination revealed numerous foci of granuloma formations with no evident exponents of dysplastic or neoplastic abnormalities (Ki67 negative immunostaining). Significant immune cell infiltrations without atypical features and scattered foam cells arranging the numerous foci of granuloma inflammation were noticed. These areas were intensively infiltrated by CD68-positive cells (macrophages), and accompanied by glomerular fibrosis (Figure 5) as well as atrophic proximal tubules (Figure 6).

Interestingly, vimentin expression in the renal parenchyma adjacent to granuloma lesions has presented a classic topography involving endothelia and tunica media of renal blood vessels (interlobular arteries and veins as well as glomerular capillaries, Figure 7).

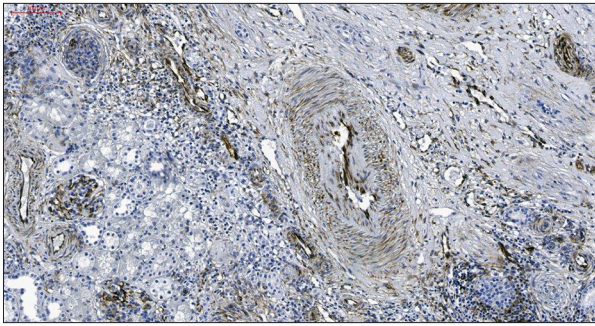


Figure 7. The immunohistochemical distribution of vimentin in the renal parenchyma adjacent to granuloma lesions with classic topography involving endothelia and tunica media of renal blood vessels (interlobular arteries and veins as well as glomerular capillaries).

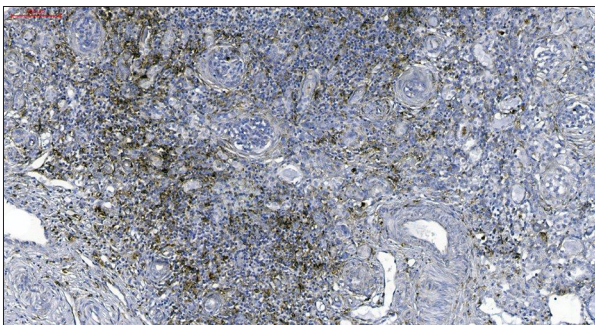


Figure 8. The areas of immune cells infiltration (with high proportion of CD68-positive cells) revealed the immunohistochemical presence of vimentin in the meshwork of leukocytes penetration forming a fiber-like structures in the closest proximity of involved glomeruli.

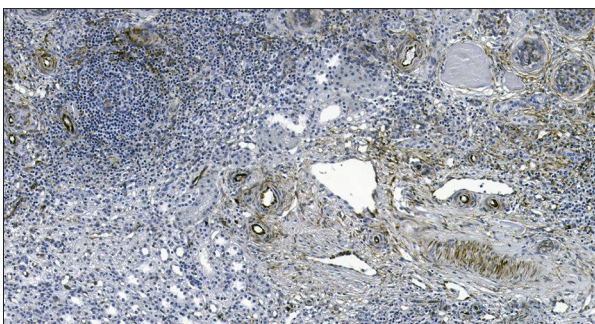


Figure 9. The immunohistochemical presence of vimentin within blood vessels, but also in the meshwork of leukocytes penetration of renal parenchyma.

The areas of immune cells infiltration (with high proportion of CD68-positive cells) revealed the immunohistochemical presence of vimentin not only within blood vessels but also in the meshwork of leukocytes penetration (Figures 8, 9) forming a fiber-like structures in the closest proximity of involved glomeruli. What is more, inflammatory glomeruli did not express

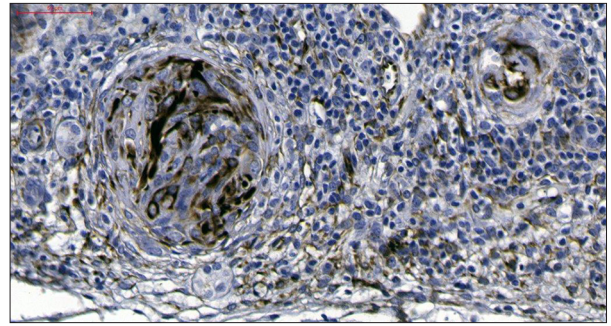


Figure 10. The renal granuloma formation with the immune cell infiltration and intensive immunohistochemical expression of vimentin within glomerular mesangium.

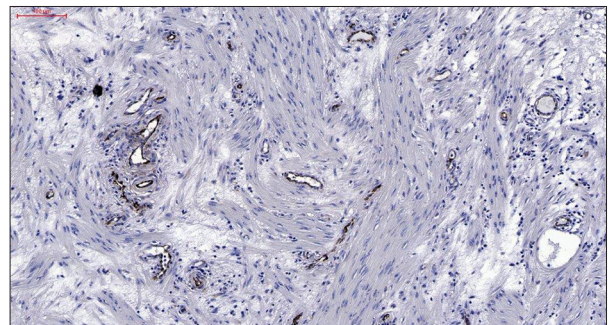


Figure 11. The area of deep renal fibrous cortex did not express vimentin within ground substance and cells of dense connective tissue. The immunohistochemical expression of vimentin is found within endothelia and, to some extent, in the network forming tunica media of blood vessels.

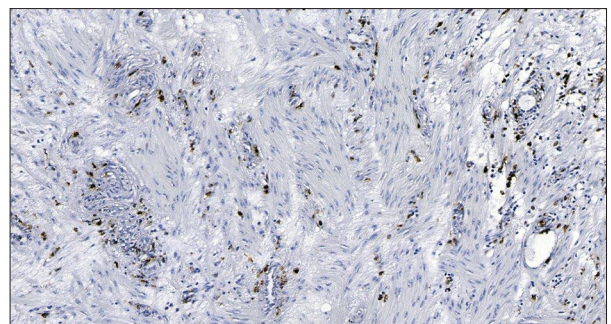


Figure 12. The serial cross-section of the fibrotic area of the renal granuloma formation with the scanty quantity of CD 68 positive macrophages.

vimentin in the restricted and atrophic vascular bed, but they presented it within glomerular mesangium (Figure 10).

Both cortical and medullar territories which were already fibrous did not express vimentin within ground substance and cells of dense connective tissue (Figure 11). Vimentin was again found within endothelia, and, to some extent, in the network forming tunica media of blood vessels. These fibrous areas were

still accompanied by CD68-positive cells infiltration, however, their concentration was smaller and they were not accompanied by extensive infiltration of immune cells (Figure 12).

Discussion

Xanthogranulomatous pyelonephritis (XP) is usually diagnosed in the late stages of the disease [1,9,10]. First of all, it is an unusual form of chronic pyelonephritis and, as was already mentioned in introduction, it is an extremely rare cause of severe kidney destruction. Most affected individuals develop recurrent fevers, anemia, and a painful kidney mass. Moreover, the disease course is long enough that compensatory hypertrophy of the healthy kidney is observed [14].

In our study, a 7-year old girl diagnosed with XP did not present with abdominal pain. No compensatory hypertrophy of the left kidney was observed. The laboratory values were within physiological ranges. Also a microscopic evaluation of kidney parenchyma revealed the areas which still were not inflammatory infiltrated or rearranged by fibrous components. Based on these observations, we assumed that the patient was diagnosed at a relatively early stage of the disease. The case was not complicated by the coexistence of other diseases. From this point of view, this particular case might help us in understanding some basic elements leading to kidney destruction as observed in a majority of XP patients.

As was already mentioned, the exact etiology of XP is still unknown. Generally, it is accepted that the disease process requires long-term renal obstruction and infection [1,4,9,10]. However, there are only a small proportion of patients who develop XP during *Proteus* or *Escherichia coli* infections. Similarly, only in single patients with a long history of kidney stones has XP been recognized. For this reason, a number of other trigger mechanisms are considered in XP pathophysiology [15]. One of them is abnormal lipid metabolism [15,16].

Interestingly, disorders in lipid metabolism in XP patients do not necessarily have to be reflected in standard laboratory tests [10,15]. These abnormalities could be expressed at the tissue level, leading to abnormal activation of macrophages [15]. All agree that the primary factor promoting morphological changes in the kidney of XP patients is uncontrolled macrophage activity [15,17].

In line with the aforementioned, we decided to examine a tissue expression of vimentin, which is a factor that attracts macrophages into areas of inflammation [18], increases their invasiveness [19] and, finally, stimulates phagocytosis [20]. In addition, during chronic inflammation, amino acid residues can be enzymatically transformed into citrulline protein residues

such as vimentin by a process called citrullination [21]. If their shapes are significantly altered to normal proteins, the proteins may be recognized by the immune system as antigens, thus exaggerating an immune response [21].

Finally, vimentin is a well-established protein involved in tissue cholesterol homeostasis and epithelial-mesenchymal transition, which are also observed at the tissue level in XP patients [22].

Taking this information together, is it possible that XP development can be induced by vimentin overexpression in renal parenchyma?

The immunohistochemical pattern of vimentin expression revealed its transient presence within leukocyte infiltration meshwork of the XP kidney. The areas which were not yet involved in XP devastation, as well as already fibrous territories, have presented vimentin expression exclusively within renal vasculature (interlobular blood vessels, glomerular tufts and peritubular capillaries). Vimentin, as studied in infiltrated areas, was expressed both in glomerular and tubular spaces; and it was accompanied by intensive macrophage presence. With the progress of fibrosis, vimentin expression was systematically decreasing and the number of CD68-positive cells was restricted.

Such a vimentin time-related and area-related topography might suggest not only its direct effect on macrophages but also profibrotic function. This observation is not unique. Several reports indicated vimentin as a promising marker of tubulointerstitial fibrosis in the early stages of chronic renal failure. Others suggest that anti-vimentin auto-antibodies in renal transplant recipients have been correlated with interstitial fibrosis and tubular atrophy [23].

We do realize that the process of kidney reconstruction in XP patients probably is not possible to stop or reverse by employing contemporary therapeutic tools. The only treatment is nephrectomy. However, in some patients with bilateral XP, saving part of the intact kidney must be taken under consideration (we have no reports describing patients who underwent a kidney transplantation after bilateral XP). Perhaps these patients would benefit more if such an operation is followed by biological treatment, including anti-vimentin antibodies [4,24].

Conclusions

Vimentin expression in XP patients confirms a focal character of chronic granuloma formation and may suggest the complexity of XP pathogenesis involves not only macrophages and fibroblasts activation but also local lipid deregulation and fibrosis.

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