



ORIGINAL ARTICLE

Oxalate nephropathy is a major cause of kidney injury in surgically treated pancreatic adenocarcinoma patients

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ABSTRACT

Background. Despite new therapeutics, the prognosis for pancreatic cancer remains poor. Pancreatic surgery is a therapeutic option in non-metastatic forms. The consequences for renal function are poorly described.

Methods. Patients who underwent surgery for pancreatic cancer between 1 January 2010 and 1 January 2017 and who experienced kidney biopsy in the Pitié-Salpêtrière Hospital were analysed.

Results. Two hundred and ninety-four patients had pancreatic surgery during the period of analysis and five of them had a kidney biopsy (mean \pm SD 20 months \pm 13.6 months after surgery) during the post-operative follow-up. Among these patients, three exhibited oxalate nephropathy (ON), indicating that the prevalence of ON in patients with pancreatectomy is at least 1%. ON may be insidious, with chronic renal failure without urinary abnormalities. All patients had a high oxalate-to-creatinine ratio in urine sample. Renal function improved after specific management of ON in two patients. Pancreaticoduodenectomy may represent a higher risk of ON than left pancreatectomy.

Conclusion. Although rare and underestimated, ON appears to be a real risk after pancreatic resection. Early detection may preserve renal function.

Keywords: chronic kidney disease, oxalate nephropathy, pancreatic adenocarcinoma, pancreatectomy, pancreatic exocrine insufficiency

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INTRODUCTION

Pancreatic adenocarcinoma is associated with high mortality. Five-year survival is low, about 5–10% depending on the study [1]. More than 10 000 new cancers of the pancreas are diagnosed each year in France. Predictions show that pancreatic cancer will probably be the second most deadly cancer in the coming decades [2]. Survival is better in patients who undergo surgical resection, which accounts for ~15% of cases only, but remains very low with 15–25% 5-year survival [3].

Although some data are contradictory, chronic kidney disease (CKD) is associated with low survival in oncology [4]. Renal dysfunction has a negative impact on the continuation of chemotherapy in patients with cancer, including pancreatic cancer. In a study of 40 patients with resected pancreatic cancer [5], renal dysfunction evaluated by glomerular filtration rate (GFR) was associated with the non-continuation of chemotherapy at 6 months: 75% versus 30% for GFR <60 mL/min versus >60 mL/min, respectively. Furthermore, there is evidence that the severity of CKD affects post-operative mortality as reported in dialysed patients compared with non-dialysed ones [5].

Data are missing about the impact of pancreas resection on renal function. In a series of 1061 patients undergoing pancreatic surgery (including 1.7% with CKD Stages IV and V), CKD was associated with an increase in post-operative complications, in particular with the occurrence of acute kidney injury (AKI) requiring haemodialysis (12 patients, odds ratio = 12.9) [6]. Nevertheless, the mechanisms of AKI were not investigated.

Multiple causes can lead to kidney failure in the management of pancreatic cancer. The main chemotherapies used in pancreatic cancers are gemcitabine, which is sometimes associated with capecitabine [3], nab-paclitaxel [7] or fluorouracil associated with irinotecan and oxaliplatin. Among these chemotherapies, gemcitabine sometimes induces a severe thrombotic microangiopathy [8, 9], and carboplatin has tubular toxicity [10]. Thrombotic microangiopathy may rarely occur as an inaugural manifestation in pancreatic cancer [11]. Repeated use of iodinated contrast products may also cause acute renal failure [12].

Oxalate nephropathy (ON) after pancreatic exocrine insufficiency (PEI) is described [13], but few data are available on renal risk after pancreatectomy. The purpose of this article is to describe clinicopathological findings in patients with both pancreatic cancer treated by surgery and renal impairment.

MATERIALS AND METHODS

Patients

This is a monocentric and retrospective study. In the pathology department of the Pitie-Salpêtrière University Hospital, all patients having a pancreatectomy between 1 January 2010 and 1 January 2017 were identified. This list of patients was compared with the list of all patients having a renal biopsy performed in the nephrology department from 1 January 2010 to 1 August 2017. The selected patients were those present in both lists.

Data analysis

All clinical data from patients were recovered from their medical records. Clinically relevant information (age, sex, date of birth, comorbidity, blood pressure, presence of diabetes, treatments, associated chemotherapy) were collected. Renal function [creatinine level and estimated GFR (eGFR) according to the

MDRD equation, before diagnosis, after surgery, during the follow-up], renal morphology and urinary analysis were reported. Patients were monitored up to the last value of creatinine available or until death.

Histological analysis

Renal pathology consisted of light microscopy analysis with Masson trichrome, periodic acid-Schiff, Jones coloration and immunofluorescence analysis with antibodies directed against IgA, IgG, IgM, C3, C1q, Kappa, Lambda and fibrinogen. Polarization test was used if necessary. Infrared microscopy (IMAGEUR—Spotlight400—PerkinElmer®) analysis was performed in Patient 1.

Compliance with ethical standards

There was no research involving human participants. Consent statements were performed when possible.

RESULTS

Between 1 January 2010 and 1 January 2017, 294 pancreas resections were analysed in the pathology department of Pitie-Salpêtrière University Hospital. All patients underwent surgery related to a pancreatic tumour. From 1 January 2010 to 8 January 2017, 1838 native kidney biopsies were performed in the nephrology department. Five patients who were in both lists were identified. The main characteristics are summarized in Table 1. Four men and one woman were identified and were 74 ± 5.4 years old. All patients underwent renal biopsy after pancreatic surgery. Surgeries were pancreaticoduodenectomy in four cases and left pancreatectomy in the fifth case. Kidney biopsies were performed (mean \pm SD) 20 months \pm 13.6 months after surgery. Serum creatinine level was 280 ± 202 μ mol/L for kidney biopsy. The main cause of identified nephropathy was ON that occurred in three of the five cases. One patient needed dialysis. During follow-up, three patients died: two due to the progression of the adenocarcinoma and one from a sepsis.

Patient 1

A 74-year-old woman with medical history of hypertension was treated by a pancreaticoduodenectomy for a non-metastatic pancreas tumour. Renal function was subnormal before surgery with an eGFR of 85 mL/min according to the MDRD equation. She was given adjuvant chemotherapy after surgery. Eleven months later, she presented with diarrhoea, local recurrence of adenocarcinoma and cholangitis. She developed AKI. Her creatinine increased from 117 to 400 μ mol/L over the course of a month and she became oliguric. Renal ultrasound showed poor corticomedullary differentiation. Dipstick showed minimal haematuria and no leucocyturia. Urinary protein-to-creatinine ratio was 0.54 g/g. Renal biopsy showed acute tubular necrosis with numerous oxalate crystals deposited in renal tubules (Figure 1A–C). Oxalate-to-creatinine ratio was 126 mg/g. Infrared microscopy confirmed oxalate crystal (Figure 2). ON was diagnosed. She started haemodialysis for 5 days/week and was treated with urinary alkalization, low-oxalate diet and calcium supplements. She recovered sufficient kidney function to stop dialysis after 2 months with an eGFR of 15–20 mL/min. She died 10 months later from progression of adenocarcinoma.

Table 1. Patients characteristics

Characteristics	Patients				
	1	2	3	4	5
Sex and age (For M, years)	F, 74	M, 75	M, 64	M, 74	M, 62
Comorbidity	HT	IHD, hypothyroidism, dyslipidaemia	DM, OSAS, HT, dyslipidaemia	DM, HT, IHD, BPH, CKD	DM
Second cancer	No	No	Prostatic adenocarcinoma	No	Bladder, prostate and kidney cancers
Surgery	PD	PD	PD	PD	Left splenopancreatectomy
Chemotherapy	Gemci/oxali/irino/5 FU	Oxali/irino/5 FU/Elvorine	Gemci	Gemci/oxali	Gemci
Renal impairment after surgery	11 months	4 months	4 months	33 months	7 months
Delay of KB after surgery	12.5 months	20 months	50 months	33 months	7 months
Drugs and medication	Perindopril, indapamide	PES, paroxetine, atenolol, ascorbic acid, levothyroxine	Atenolol, repaglinide, sitagliptin, PES	Bisoprolol, trimetazidine, alfozozine, insulin, PES	Aspirin, ticagrelor, ramipril, bisoprolol, insulin, rosuvastatine
MDRD, mL/min					
Before surgery	85	79	78	44	52
Before KB	54, 37 at 11, 12 months, respectively	67, 35 at 4, 18 months, respectively	51, 40 at 6, 41 months, respectively	39, 34 at 21, 26 months, respectively	45 at 6 months
At KB	8 (haemodialysis)	33	31	6 (haemodialysis)	21
Urinary analysis at diagnosis	17 after 2 month dialysis	33, 6 months after biopsy	25–30, 8 months after biopsy	Haemodialysis dependent	37
Protein-to-creatinine ratio	0.54 g/g	0.07 g/g	0.3 g/g	0.54 g/g	7.6 g/g
Na fractional excretion	4.99%	1.2%	2.5%	18.1%	—
Red blood cells	19/mm ³	7/mm ³	6/mm ³	14/mm ³	35/mm ³
White blood cells	13/mm ³	6/mm ³	6/mm ³	1/mm ³	19/mm ³
Oxalate per day	—	115 mg ^a	118 mg	—	—
Oxalate-to-creatinine ratio	126 mg/g	78.7 mg/g ^a	98 mg/g	—	—
Renal imaging					
Kidney length	10 cm each	11 cm each	10.5 cm each	Right 9.6 cm, left 8 cm	Single left kidney 13 cm
Renal lithiasis	No	No	Left renal microlithiasis	No	No
Obstruction	No	No	No	No	No
Biopsy findings					
Glomeruli	16 NI glomeruli	16 (14 NI, 1 sclerotic, 1 FSGS)	24 (14 NI, 2 sclerotic, 8 ischaemic)	6 (2 NI, 4 sclerotic)	4 (2 NI with thickened mesangium, 2 sclerotic)
Tubule	Acute tubular necrosis	Acute tubular necrosis	Acute tubular necrosis	Acute tubular necrosis.	Acute tubular necrosis
Interstitial	Interstitial fibrosis 5%	Interstitial fibrosis 20%	Extensive interstitial fibrosis	Diffuse interstitial fibrosis	Interstitial fibrosis
Vessels	Subnormal vessels	Endarteritis and arteriolar hyalinosis	Moderate to severe hyalinosis	Severe vascular lesions	Moderate hyalinosis
Crystal	Polarizing crystals of rhomboid aspect	Numerous calcium oxalate crystals	One birefringent crystal	No	No
Immunofluorescence	Negative	Negative	Negative	Negative	IgA and C3 mesangial deposits
Follow-up					
Kidney function	Haemodialysis 2 months then resumed	GFR stabilization 6 months thereafter	Variable GFR 8 months after biopsy	Dialysis dependent	Stage 3b CKD
General	Death 10 months after	Alive	Alive	Death 2 months later	Death 2 years after cancer diagnosis

^aFew weeks after ascorbic acid withdrawal.

PD, pancreatectoductectomy; F, female; M, male; HT, hypertension; KB, kidney biopsy; IHD, ischaemic heart disease; DM, diabetes mellitus; OSAS, obstructive sleep apnoea syndrome; BPH, benign prostate hypertrophy; PES, pancreas enzyme supplementation; Gemci, gemcitabine; Oxali, oxaliplatin; Irino, irinotecan; 5 FU, fluorouracil; NI, normal; FSGS, focal segmental glomerulosclerosis.

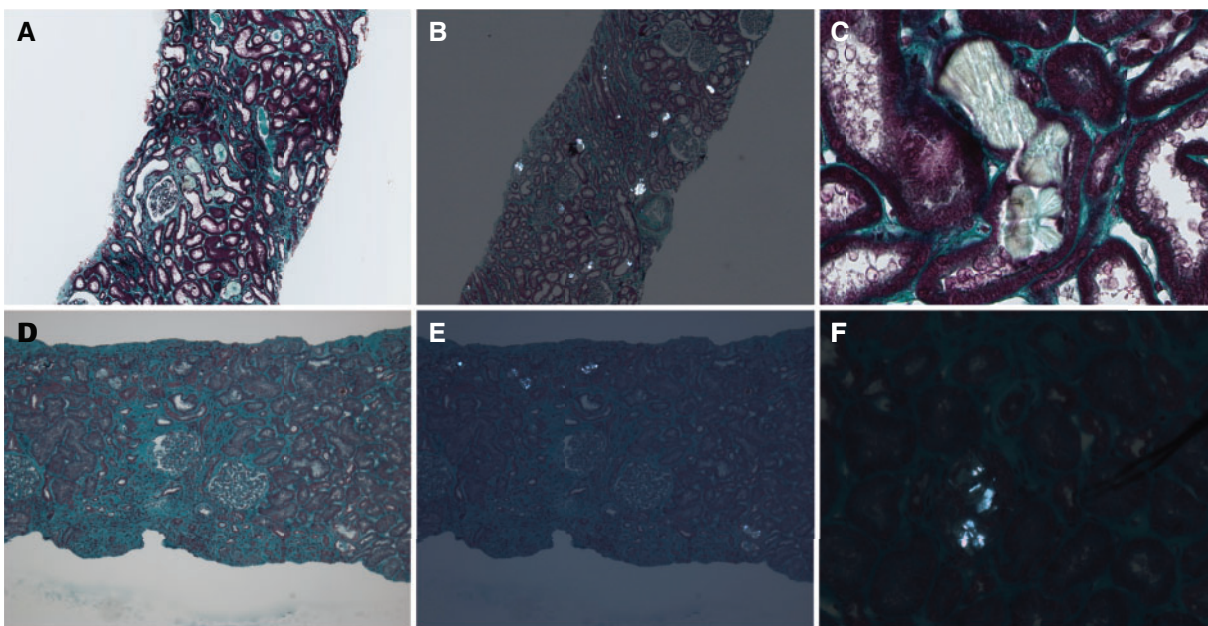


FIGURE 1: Kidney biopsies of Patients 1 and 2. (A–C) Kidney biopsy of Patient 1. (A) Kidney section showing severe tubular lesions (Masson trichrome stain, magnification $\times 200$). (B) Light microscopy under polarized light revealing several calcium oxalate crystals (magnification $\times 200$). (C) Oxalate crystal with rhomboid aspect (Masson trichrome stain, magnification $\times 400$). (D–F) Kidney biopsy of Patient 2. Moderate tubular lesions, interstitial fibrosis and oxalate crystal without (D) and with (E) polarized light (Masson trichrome stain, magnification $\times 200$). (F) Oxalate crystal under high magnification and polarized light (Masson trichrome stain, magnification $\times 400$).

Patient 2

A 76-year-old man with dyslipidaemia and ischaemic heart disease presented with pancreatic head cancer. Treatment with chemotherapy FOLFIRINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin) followed by pancreaticoduodenectomy and consolidation chemotherapy by LV5FU2 (fluorouracil, leucovorin) was proposed. Renal function was normal during surgery (eGFR was 90 mL/min according to the MDRD equation). He had a very progressive degradation of renal function with regular loss of eGFR: 67 mL/min at 4 months, 60 mL/min at 6 months, 45 mL/min at 14 months, 33 mL/min at 18 months when a kidney biopsy was performed. Several urinary examinations revealed no significant proteinuria, no haematuria and no leucocyturia. Renal ultrasound was normal. He was treated with atenolol, acetylsalicylic acid, levothyrox, paroxetine, pancreatic enzyme supplements 75 000 UI/day (since the surgery) and self-medicated with ascorbic acid 500 mg/day. Blood pressure was 136/86 mmHg. He reported chronic diarrhoea without weight loss. Renal biopsy revealed interstitial fibrosis associated with numerous oxalate crystals (Figure 1D–F). After discontinuation of ascorbic acid, hyperoxaluria was confirmed (115 mg/24 h and oxalate-to-creatinine ratio was 78.7 mg/g). He was treated with ascorbic acid removal, low-oxalate dietary, calcium supplementation and potassium citrate supplementation. Renal function stabilized and 6 months after the biopsy eGFR remained at 33 mL/min without worsening.

Patient 3

A 64-year-old man with a 15-year history of type 2 diabetes, hypertension and obstructive sleep apnoea was referred because of impaired kidney function. Four years earlier, he had a pancreatic head tumour treated with pancreaticoduodenectomy and gemcitabine. Renal function was normal at the time of surgery (eGFR was 92 mL/min according to the MDRD equation) and started to

decrease 4 months later (66 mL/min). While GFR decreased progressively, a kidney biopsy was performed >4 years after the surgery (eGFR was 30 mL/min). He did not exhibit any leucocyturia, haematuria or significant proteinuria at the time of biopsy. Computed tomography showed a non-obstructive microlithiasis on the right kidney. Renal biopsy showed mixed lesions with 24 glomeruli including 1 sclerotic glomerulus. Significant fibrosis (70% of the biopsy area) was notified. Vascular lesions were not severe. A single crystal of oxalate was seen. Urinary tests at the time of biopsy confirmed the presence of hyperoxaluria at 118 mg/24 h or 98 mg/g oxalate-to-creatinine ratio, consistent with—at least in part—the diagnosis of ON. Adequate diet was proposed and then GFR had stabilized around 25–30 mL/min within 8 months.

Patient 4

A 74-year-old man with medical history of diabetes mellitus and unexplored CKD (eGFR was 45 mL/min according to the MDRD equation) had a tumour to the head of the pancreas treated with pancreaticoduodenectomy and chemotherapy (gemcitabine, oxaliplatin) during numerous cures. GFR was stable during 2.5 years after surgery. He exhibited asthenia, loss of appetite revealing acute renal failure (serum creatinine was 522 μ mol/L) without haematuria or leucocyturia. Proteinuria-to-creatinine ratio was 0.54 g/g. Blood pressure was at 133/70 mmHg and he was oliguric. A renal biopsy was performed, but small in size with only six glomeruli, of which four were sclerotic. Tubulointerstitial study showed non-specific lesions with tubular necrosis, interstitial fibrosis associated and vascular lesions. Haemodialysis was started and 2 months after he died from sepsis during the use of chemotherapy.

Patient 5

A 62-year-old man had a long history of cancer and diabetes mellitus. In the surveillance of kidney cancer, an

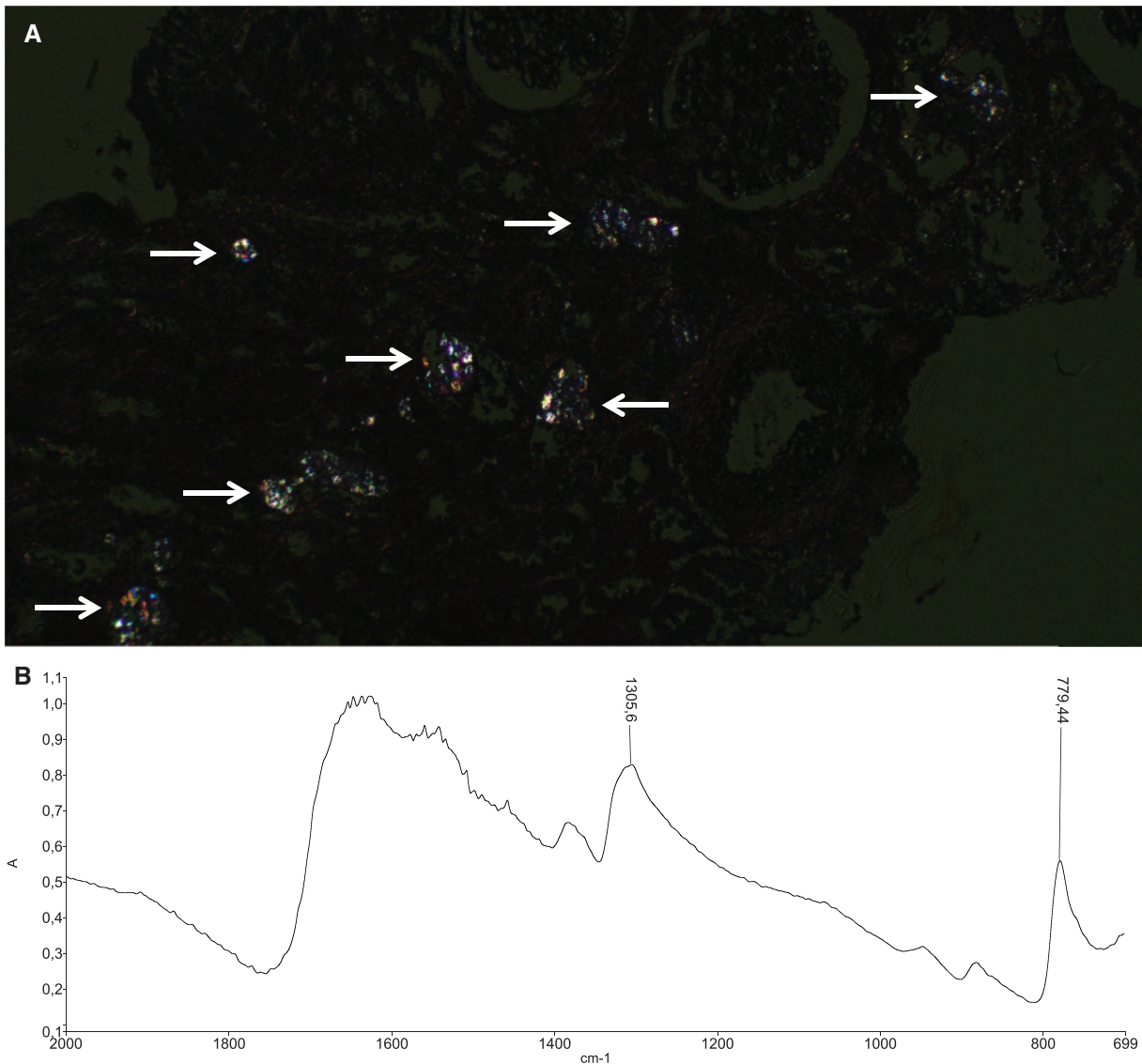


FIGURE 2: Infrared microscopy analysis of Patient 1. (A) Many birefringent crystals under polarized light (magnification $\times 200$). (B) Infrared microscopy analysis showing two peaks that are typically characteristic of calcium oxalate monohydrate (whewellite), consistent with ON.

adenocarcinoma of the tail of the pancreas was diagnosed. He underwent a left splenopancreatectomy followed by eight courses of gemcitabine. During chemotherapy, he had pneumonitis and severe respiratory distress requiring orotracheal intubation. In this context, acute renal failure occurred with creatinine level at $280 \mu\text{mol/L}$ associated with haematuria ($35/\text{mm}^3$) leucocyturia ($19/\text{mm}^3$) and protein-to-creatinine ratio was 7.6 g/g (creatinine level was $130 \mu\text{mol/L}$ before surgery attributed to a single kidney). A kidney biopsy was performed, but the interpretation was quite difficult because of few glomeruli (four including two sclerotic). Both glomeruli showed an ischaemic appearance with a thickened mesangium. Fibrosis represented 20% associated with severe lesion of acute tubular necrosis. Immunofluorescence found moderate deposits of IgA and rare C3, consistent with IgA nephropathy worsened by acute tubular necrosis. He died 2.5 years after renal biopsy (creatinine level was $200 \mu\text{mol/L}$) despite chemotherapy resumption.

DISCUSSION

In this first study focusing on renal dysfunction after pancreatic cancer surgery, the main nephropathy is ON (usually a relatively uncommon kidney disease), which occurred in three out of the five cases. The other two patients did not have a pancreatic cancer-related nephropathy. ON diagnosis led to discontinuation of dialysis in one patient and stabilization of renal function in another.

Prevalence of ON

The occurrence rate of ON after pancreatic cancer surgery can be estimated to be at least 1% (three cases among 294 patients). This rate is underestimated because (i) acute kidney failure in oncology is mainly assumed to be related to dehydration, tubular necrosis or drug induced: kidney biopsies are poorly

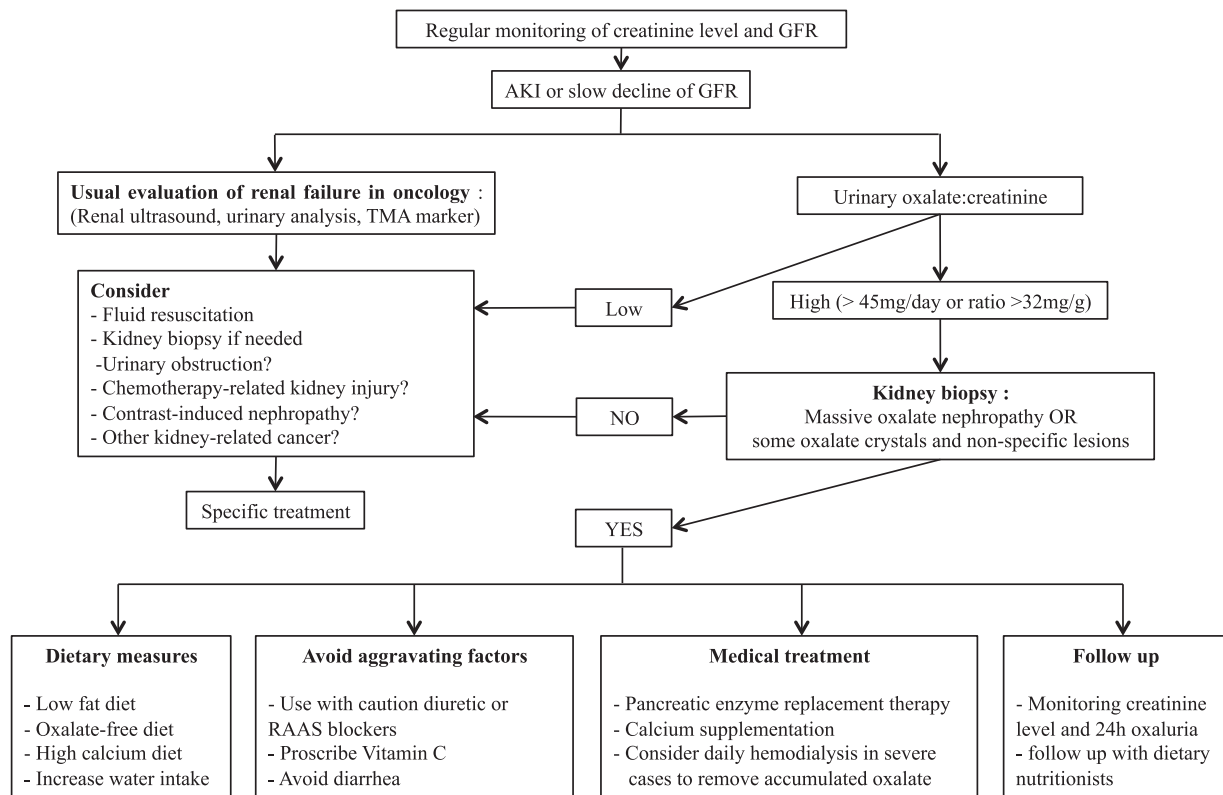


FIGURE 3: Proposed management of renal failure in patients with resected pancreatic cancer. RAAS, reninangiotensinldosterone system.

performed in this context; (ii) ON is rare and poorly recognized; and (iii) clinical presentation maybe insidious with a slow loss of eGFR without any obvious urinary abnormality (absence of leucocyturia and haematuria, low proteinuria), able to mimic vascular nephropathy in old patients who often have high blood pressure.

Clinical heterogeneity of ON

Hyperoxaluria may manifest as lithiasis, severe acute renal failure or insidious kidney failure. ONs can be divided into three groups: primary hyperoxaluria, which is related to inborn errors of metabolism (genetic origin); toxic hyperoxaluria related to certain substances rich in oxalate or oxalate precursor such as ethylene glycol [14], vitamin C [15], star fruit [16] or certain juices [17]; and enteric hyperoxaluria. Numerous causes of enteric hyperoxaluria are described, including: loss of colonization by *Oxalobacter formigenes* [18], Crohn's disease [19], bariatric surgery like Roux-en-Y Gastric bypass [20] or jejunoileal bypass [21], short bowel disease and exocrine pancreatic insufficiency [13].

The pathophysiology of ON is well identified in these digestive diseases. In basal state, calcium binds to oxalate in the intestinal lumen creating insoluble calcium oxalate complexes, which limit oxalate absorption. During digestive malabsorption, free fatty acid will bind to calcium, thus inhibiting the formation of calcium oxalate complexes. As a consequence, digestive absorption of oxalate will be increased, leading to high-oxalate plasma level and high-oxalate urinary concentration, exposing patients to the risk of ON.

Pancreas and ON

Twelve patients with ON and chronic pancreatic disease from four French centres were identified by Cartery et al. [13]. Pancreatitis was related to alcohol consumption, but no cancer was reported. Enteric hyperoxaluria (urine oxalate-to-creatinine ratio was >32 mg/g) concerns about one-quarter of patients with chronic pancreatitis [22]. Only one case of ON associated with pancreatic cancer without pancreatectomy has been described [23]. The rarity of this entity may be explained by the fact that ON is usually a late complication of malabsorption, and patients with unresectable pancreatic cancer have a very limited life span. Chronic ON associated with pancreatectomy has already been described in a case report by Mahajan et al. [24] in a 54-year-old woman who developed a CKD 7 years after pancreatectomy, and the diagnosis of ON helped to improve renal function.

PEI and pancreas adenocarcinoma

The occurrence of ON in our series may be consecutive to the surgery itself, but may also be related to pancreatic insufficiency associated with the pancreatic tumour. No data are available for hyperoxaluria and pancreas adenocarcinoma. According to Bartel et al.'s [25] review, PEI occurs in 46–100% of patients with resectable pancreatic cancer. The rate of PEI following surgery (like pancreaticoduodenectomy) is high (70–100%). In a prospective study, Sikkens et al. [26] studied exocrine pancreatic function in 29 patients with resectable pancreatic adenocarcinoma. Among these patients, 13 patients had PEI before

surgery. After a median follow-up of 6 months post-surgery, all but five patients had PEI. It is likely that hyperoxaluria should be frequent in these patients.

Due to the preservation of the duodenum, distal pancreatectomy is less associated with PEI (30–66%). It can be noted that Patient 5, who underwent a splenopancreatectomy, did not develop any ON.

Interestingly, a recent study in France [27] analysed PEI in patients undergoing surgery for a benign pancreatic tumour. PEI was very rare before surgery (only 3 patients out of 92), but post-operative PEI was high (61% of the patients). These patients may be considered at risk of ON.

Do not forget ON

Based on this clinical study, several points should be noted:

- ON is not limited to AKI, but may manifest as a slow and progressive renal dysfunction over several months or years even in the absence of urinary abnormality (Patients 2 and 3);
- clinical (diarrhoea, fatty stools) and biological signs (high 24-h oxaluria or oxalate-to-creatinine ratio, fecal elastase) of PEI should be suggestive of ON;
- ON diagnosis may be difficult during pathology study. A single oxalate crystal associated with hyperoxaluria without evidence of other kidney disease is consistent with ON diagnosis. Polarized light examination should be systematic.

ON treatment

Some conditions may worsen renal function during ON. Diarrhoea, for example, by lowering the GFR, can increase the precipitation of crystals. Certain foods (tea, coffee) or even medicines like ascorbic acid (Patient 2) can aggravate ON by increasing the oxalate level.

Numerous measures contribute to reduce the intestinal oxalate level. Indeed, a low fat and oxalate diet, high fluid intake, calcium intake several times a day and pancreatic enzyme supplementation may be helpful. Increasing GFR by stopping the renin-angiotensin system blockers and improving diarrhoea are very important in order to reduce hyperoxaluria. Management of kidney injury among patients with resectable pancreatic cancer is summarized in [Figure 3](#).

CONCLUSION

In summary, ON can occur in at least 1% of patients with operable pancreatic cancer. Patients who experienced AKI or slowly progressive CKD in such cases even without urinary anomaly should benefit from a urinary oxalate-to-creatinine ratio and a kidney biopsy if necessary. Early diagnosis is important because specific management can improve or stabilize renal function. Physicians should be aware of this underestimated complication.

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CONFLICT OF INTEREST STATEMENT

None declared.

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