DECOMPENSATED DIABETES MELLITUS BINOMIAL - EMPHYSEMATOUS PYELONEPHRITIS AND PERIODONTAL DISEASE

Cristiana-Elena Vlad[1], Liliana Foia[2]*, Cosmin-Alexandru Agache[3], Ștefan-Adrian Strungaru[4], Vasilica Toma[2], Amelia Surdu[2], Ancuța Goriuc[2], Laura Florea[6]

[1]Section of Internal Medicine, Hospital "Dr. C. I. Parhon", Bulevardul Carol I 50, Iași, Romania
[2]"Grigore T. Popa" University of Medicine and Pharmacy, Iași, Faculty of Dentistry, Department of Surgery
[3]Section of Urology, Hospital "Dr. C. I. Parhon", Bulevardul Carol I 50, Iași, Romania
[4]Department of Research, Faculty of Biology, "Alexandru Ioan Cuza" University, Iasi, România
[5]"Grigore T. Popa" University of Medicine and Pharmacy, Iași, Faculty of Dentistry, Department of Implantology, Oral Rehabilitation
[6]"Grigore T. Popa" University of Medicine and Pharmacy, Iași, Faculty of Medicine, Department of Nephrology-Internal Medicine

***Corresponding author** Liliana Foia, , email: lilifoia@yahoo.co.uk

ABSTRACT

Introduction: Periodontal disease and emphysematous pyelonephritis, 2 independent pathologies, were determined by ineffective blood glucose monitoring. Emphysematous pyelonephritis is commonly associated with diabetes, especially in women, with impaired immune system and urinary tract obstruction, which subsequently over-infects. Predisposing factors are: diabetes mellitus, end stage renal disease, immunosuppression, urinary tract obstruction, and rarely polycystic kidney disease. Periodontitis is an inflammatory disease of the gum and deep periodontal tissues, preceded and accompanied by gingivitis. The primary etiology of the periodontal lesion is anaerobic, gram-negative bacteria: *Aggregatibacter actinomycetemcomitans, Tannerella forsythensis, Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, Campylobacter rectus, and Treponema denticola*. **Clinical-case:** A 71-year-old patient known for complex pathology addressed our clinic due to *lower urinary tract symptoms* (pollakiuria, dysuria). The clinical examination reports: overall influenced condition, afebrile, at the level of the oral cavity: generalized inflammation, gingival recession, plaque deposits, small bleeding, swelling and inflammation, abnormal gingival anatomy owing to tissue destruction. Chemistry panel reveals *inflammatory syndrome*, metabolic acidosis, *hyperglycemia*, pathological *urinalysis (leukocyturia*, hematuria, microbial flora, ketone bodies), and urine culture positive for E. coli, *multidrug resistant* (sensitive to Meropenem, Linezolid). The medical imaging (abdominal ultrasound, *abdominopelvic* CT scan with contrast medium) show lesions associated with emphysematous pyelonephritis. Corroborating the anamnestic, clinical and paraclinical data, the patient was diagnosed with right emphysematous pyelonephritis, periodontal disease and diabetic ketoacidosis.

Conclusion: After early initiation of the maximum therapeutic regimen (antibiotic therapy, double J stent and percutaneous nephrostomy), the patient presented a worsening in dynamic of the general condition, chemistry panel and imaging aspect (disorganization of the renal architecture, gas bubbles) the reason why radical nephrectomy was required. Clinical-biological post-operative evolution was good. Adjustment of glycemic values in diabetic patients result in improvement of the periodontal disease symptomatology.

Keywords: Emphysematous pyelonephritis, periodontal disease, diabetic ketoacidosis

INTRODUCTION:

Emphysematous pyelonephritis (EPN) is a necrotizing kidney infection consisting of the accumulation of gas in the kidney tissue, most commonly caused by *Escherichia coli* and *Klebsiella pneumoniae*. Predisposing factors are: diabetes mellitus, end stage renal disease, immunosuppression, urinary tract obstruction, and rarely polycystic kidney disease (1).

Hyperglycemia is also associated with the occurrence of periodontal disease, being considered a complication of type 2 diabetes alongside target organ damage: peripheral nervous system, circulatory system and kidneys (2).

CASE-REPORT:

A 71-year-old patient known for metabolic (type 2 insulin-dependent diabetes

mellitus, *uncontrolled*, complicated with sensorimotor peripheral polyneuropathy, class 2 obesity), cardiovascular (stage 3 hypertension, *hypertensive heart disease*), neurological (*transient ischemic attack*), respiratory tract (chronic bronchitis) and digestive tract pathology (chronic gastroduodenitis, gastroesophageal reflux disease) addressed our clinic due to *lower urinary tract symptoms* (pollakiuria, dysuria).

The clinical examination reveals: overall influenced condition, afebrile, height = 160 cm, weight = 100 kg, body mass index = 39.1 kg / m², paleness of *skin and mucous membranes*, normal cardiopulmonary examination, *arterial* blood *pressure* (*BP*) = 140 / 80 mmHg, pulse = 86 / min. At the level of the oral cavity: generalized inflammation, gingival recession, plaque deposits, small bleeding, swelling and inflammation, abnormal gingival anatomy owing to tissue destruction, abdomen painless to palpation and increased due to *panniculus*, pollakiuria, amber urine and normal intestinal transit.

Chemistry panel: acute *azotate retention* (creatinine = 1.98 mg / dL, urea = 119 mg / dL), metabolic acidosis (serum HCO_3 - = 10 mmol / L), hyponatremia (Na = 128 mmol / L), hyperkalemia (K = 5.29 mmol / L), *hyperglycemia* (672 mg / dL), hyperuricemia (uric acid = 9.3 mg / dL), hypoproteinemia (total protein = 53 g / L), anemia (Hb = 7.5g / dL), inflammatory syndrome (neutrophilic leukocytosis, reactive thrombocytosis, erythrocyte sedimentation rate = 140 mm / h, fibrinogen = 6.48 g / L, C-reactive protein 15.5 mg / dL, procalcitonin = 4.5 ng / mL), pathological *urinalysis* (*leukocyturia*, hematuria, microbial flora, ketone bodies), proteinuria < 1g / L / 24h and urine culture positive for *E. coli*, *multidrug resistant* (sensitive to Meropenem, Vancomycin, Linezolid).

The abdominal ultrasound revealed increased right kidney size with multiple hyperreflectogenic images grouped beneath the capsule and across the renal contour, alternating with hypoechogenic, nonhomogeneous, clustering areas that develop predominant in the lower pole. Initial *abdominopelvic computed tomography*, with contrast medium, revealed at the right kidney a nonhomogeneous, imprecisely delimited fluid collection with gas bubbles on the interior (24/43/29 mm), which thickens the pararenal fascia, infiltrating the peritoneal fat in the neighborhood and deforming the underlying renal parenchyma (Fig. 1-4).

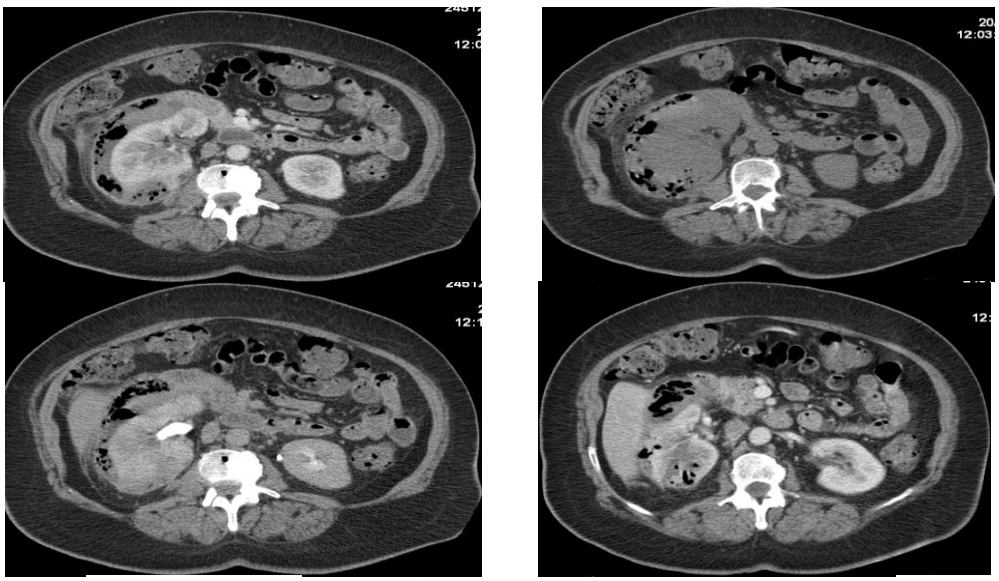

Fig. 1-4. *abdominopelvic* CT scan (native T1, native T2, after contrast medium injection, 10 minutes from contrast medium administration).

Corroborating the anamnestic, clinical and paraclinical data, the patient was diagnosed with right emphysematous pyelonephritis, periodontal disease and diabetic ketoacidosis.

The initial therapeutic strategy consisted of hydration, intravenous insulin therapy (6 IU / h), antibiotic therapy (Meropenem in combination with Vancomycin and Metronidazole), *fluoroscopic-assisted* insertion of a 6 Ch double J stent to the right kidney and right lumbar drainage with a 14 Ch percutaneous nephrostomy probe.

Given the worsening clinical and biological picture, the changes to the right kidney imagistic examination (*abdominopelvic* ultrasound reveals the disorganization of the renal architecture with nonsystematic reflective images, the absence of mobility on the psoas; control *abdominopelvic* CT scan - a nucleus of gas bubbles, communicating with a subcapsular collection and gas bubbles, a similar *arch-like* collection at the level of the right perirenal fascia, following the convexity of the kidney- Fig. 5-10), it was decided to perform radical nephrectomy.

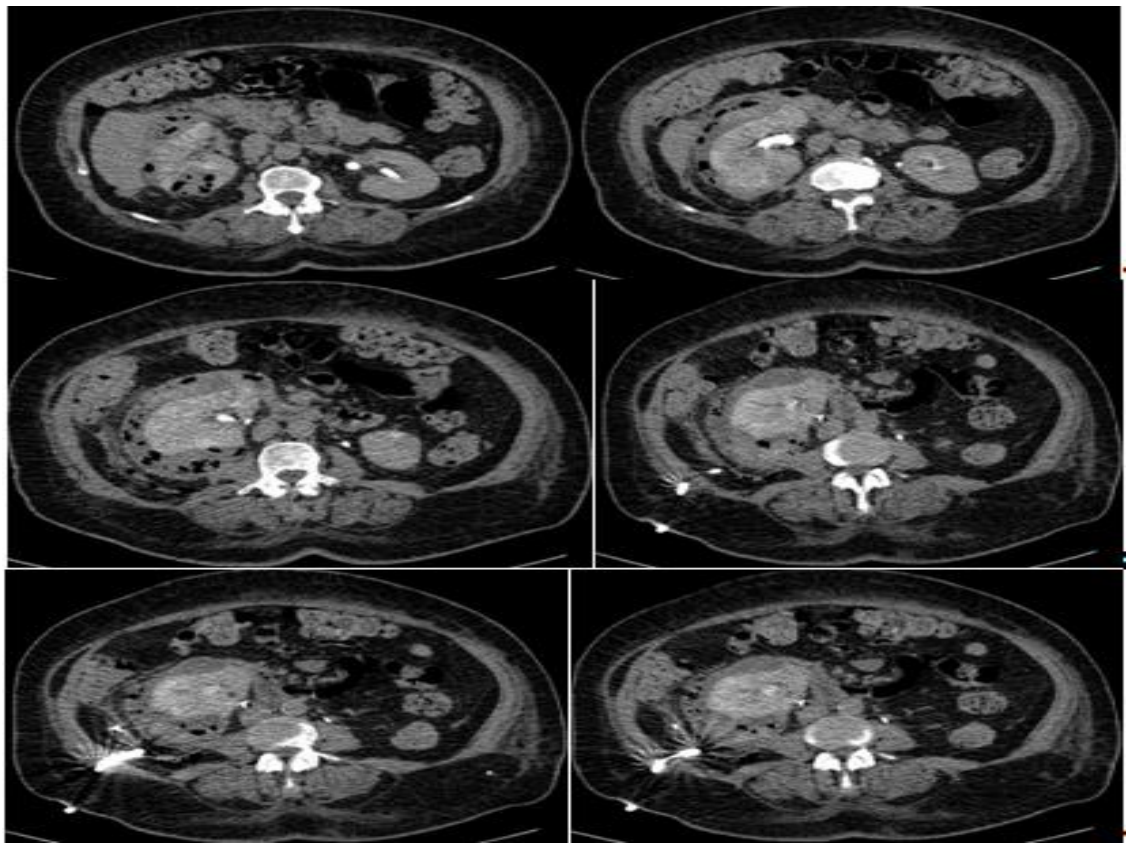

Fig. 5-7. *abdominopelvic* CT scan with contrast medium: a nucleus of gas bubbles, communicating with a subcapsular collection and gas bubbles, a similar *arch-like* collection at the level of the right perirenal fascia.

Fig. 8-10. *abdominopelvic* CT scan with contrast medium: extremity of the right lumbar drainage tube found in the posterior pararenal space and angled at the border with the perirenal fascia.

Postoperative progression was favorable with improvement in the overall clinical symptomatology, a downward trend in *azotate retention* (creatinine = 0.73 mg / dL), increase in hemoglobin (Hb = 10.5 g / dL), significant decrease of the inflammatory syndrome, the absence of electrolyte and acid-base imbalances.

The anatomopathological examination revealed macroscopic and microscopic aspects of acute suppurative pyelonephritis (macroscopically: cortical and medullary with preserved architecture, haemorrhagic renal papules, renal capsule with hemorrhagic areas, clots, purulent deposits; microscopic: cortical and medullary with large areas of polymorph inflamatory infiltrate, bounded by young granulation tissue, extensive areas of necrosis, haemorrhage, congestion and interstitial edema; the tubular component with a general aspect of compensatory dilatation, rare hyaline cylinders, tubular necrosis, and at the medullary level there is tubular atrophy, interstitial fibrosis.

DISCUSSIONS:

The emphysematous piolonephritis is commonly associated with diabetes, especially in women, with impaired immune system and urinary tract obstruction, which subsequently over-infects (3).

Sokhal et al. have found that EPN has become a relatively frequent renal pathology due to the use of imaging (renal ultrasound, abdominal CT), increased prevalence of diabetes and metabolic syndrome (4).

Aswathaman et al. have identified that EPN pathogenesis is multifactorial, having causal factors: renal vascular damage, urinary stagnation, and their association with diabetes mellitus was observed in approximately 90% of cases and in 20% with urinary tract obstruction (5). Gram negative bacteria, optionally anaerobic: *E. Coli* and other species that can cause mono or polymicrobial infections: *Klebsiella*, *Proteus*, *Pseudomonas*, *Clostridium*, *Streptococcus*, *Candida*, *Aspergillus*, *Cryptococcus* (6) are responsible for gas production by fermenting glucose and lactate. This process results in the production of high levels of carbon dioxide and hydrogen that accumulate at the site of inflammation. In this regard, Huang and Tseng, have found that carbon dioxide and hydrogen are the main constituents, together with nitrogen, oxygen, traces of ammonia, methane and carbon monoxide (1), following the sampling with a fine needle of the gas released by the tissues. Local necrosis and vascular disorders caused by infection can contribute to the formation of gas bubbles (7).

Hypoalbuminemia, shock, bacteremia, hemodialysis and polymicrobial infections, according to Lu YC et al., are predictors of mortality in EPN patients and more than two prognostic factors have the highest mortality risk, requiring immediate diagnosis and aggressive management (8). Thus, the mortality rate was 27% in the presence of a single risk factor, 75% in the presence of at least 2 and 100% in the case of the occurrence of at least 3 risk factors (5). Also, Huang JJ. and Tseng CC. reported as possible complications: thrombocytopenia (46%), kidney *failure* (35%), shock (29%), and impaired consciousness (19%) (1).

Emphysematous pyelonephritis is mostly identified through imaging techniques, because most clinical and laboratory observations will only indicate sepsis of renal origin. A simple kidney radiography (with an accuracy of 65%) shows an abnormal shadow of gas on the renal projection area, which may raise a suspicion of pathology; while renal ultrasound (69% accuracy) or abdominal CT scan will confirm the presence of intrarenal gas, according to a study by Huang and Tseng. Abdominal CT with contrast medium is preferred because it is more sensitive and defines the extent of pathology by identifying the features of renal parenchyma destruction (1). According to their results, EPN can be divided into four classes, class 1: gas in the collector system, class 2: gas restricted only to renal parenchyma, class 3A: perinephritic gas expansion or abscess, class 3B: gas extension after the Gerota fascia and class 4: bilateral EPN or EPN on a single kidney; thus, our patient may be included in Class 3A (with gas expansion at the fascia level) (1).

At the same time, the anatomopathological examination of the kidney reveals the features of abscess formation, micro- and macro-infarction, vascular thrombosis, numerous spaces

containing gas, and necrosis zones surrounded by acute or chronic inflammation (1). Some authors concluded that at microscopic level the vessels retained normal architecture and no neoformation vessels appeared, as is the case in kidney tumors (9).

A case-control study involving 74 patients diagnosed with emphysematous pyelonephritis, divided into responders (who responded successfully or with symptomatic relief to antibiotic treatment, percutaneous drainage) and non-responders (worsening of the general condition after 48 hours from fitting the pigtail catheter, nephrectomy, death), concluded that the most common symptoms were fever, lumbar pain, while the most common comorbidities were diabetes (85.14%) and urolithiasis (32.4%). In non-responder patients compared to the responders, anemia, thrombocytopenia, proteinuria (> 3g/L/24h) and positive urine cultures (4) were identified. Our patient, according to the classification made by Sokhal et al., may fall into the non-responder group due to the presence of anemia, proteinuria, *multidrug resistant E. coli* urine culture, the changes to the imagistic examination, thus requiring radical nephrectomy.

In 22 diabetic EPN patients diagnosed with the aid of abdominal ultrasound, Pontin et al. found that this pathology occurred predominantly in females, insulin dependent patients, and those treated with oral antidiabetic agents, without any evidence of obstruction in the ureter. Dehydration and diabetic ketoacidosis have been common (10). Although a high level of glucose can provide a favorable environment for the growth of bacteria that produce the gas, diabetes was not associated with increased mortality even in patients with poorly controlled diabetes (HbA1c > 8%) (11).

A retrospective study involving 38 EPN patients identified two types of this pathology. Type I was characterized by the destruction of renal parenchyma either with the absence of the liquid accumulation or with the presence of non-homogeneous, marbled type gas, while type II presented renal or perirenal fluid buildup or gas bubbles. Type I EPN had an increased mortality rate (69%) and a significantly shorter interval from clinical onset to death compared to type 2 (18%), according to Wan et al (3). Our patient, following abdominal ultrasound and abdominal CT scans, was type II, with less fulminant development and a low mortality rate.

Management options ranging from the conservative approach (volemic and inotropic support, antibiotic treatment, glycemic control) to appropriate urinary drainage and radical nephrectomy in refractory cases (4) are available. Falagas ME et al. considers that it is important to maintain a systolic blood pressure greater than 100 mmHg, volemic and inotropic support if necessary. The meta-analysis of risk factors affecting the mortality rate concluded that a 90mmHg systolic blood pressure negatively affected the mortality rate as compared to a *BP* greater than 100 mmHg. If the clinical and paraclinical condition progressively deteriorates, the level of care should be increased because these patients may require multi-organ support (12). Aminoglycosides, β-lactamase inhibitors, cephalosporins and quinolones can be used, guided by epidemiological studies specific to each region, according to a study by Khaira et al. A combination of aminoglycoside with any of the other three antibiotic groups can be used in the initial treatment stage, and after the result of the urine culture with antimicrobial sensitivity the antibiotic can be modified depending on the type, number of microorganisms and specific antibiotics (13).

In a retrospective study, which included 93% diabetic patients, Aswathaman et al. revealed that antibiotic-only treatment had a 40% success rate, while the combination of percutaneous drainage with antibiotics was successful in 80% of cases. Radical nephrectomy was not used as a first-line therapeutic course (5).

Traditionally, until the late 1980s, there has been radical nephrectomy in emergency and/or surgical drainage in combination with antibiotic treatment. In determining this

indication, the degree of renal destruction was more relevant compared to the extent of gas bubbles (7).

In the past two decades, the mortality associated with EPN has decreased to 21% due to the large-scale use of percutaneous drainage. In most cases, they only received antibiotics or needed percutaneous drainage in combination with antibiotics. Of the 32 patients diagnosed with EPN over a period of 10 years, who addressed a Japanese hospital, only 6 patients were ultimately subjected to nephrectomy (it was done for prolonged fever and sepsis), and 5 to percutaneous drainage. Clinical or biological characteristics that could predict the necessity of nephrectomy could not be identified (8). The implementation of percutaneous drainage techniques through a nephrostomy probe (pigtail with a caliber of at least 14 Ch, under ultrasound guidance) has facilitated the reduction of nephron damage and lessened renal function impairment (14).

Somani et al. demonstrated that of all the treatment strategies percutaneous drainage associated with antibiotherapy had the lowest mortality rate of 13.5%, whereas antibiotherapy alone and nephrectomy in combination with antibiotherapy had a mortality rate of 50% and 25 % (15).

This surgery can be done classic (open) or laparoscopic (with reduction in recovery and post-operative hospitalization) (16). As for our patient, even if the treatment for EPN class 3 (antibiotic in triple combination and maximal drainage: double J stent and percutaneous nephrostomy) was established, due to a worsening clinical and biological picture, the changes in the imagistic examination, it was necessary to practice radical nephrectomy. Depending on the existence of an overlapping renal pathology and the number of functional nephrons after the surgical intervention, patients may require renal support (dialysis), with a reduction in morbidity-mortality (11).

Periodontitis is an inflammatory disease of the gum and deep periodontal tissues, preceded and accompanied by gingivitis. Periodontitis implicates the destruction of gingival and periodontal connective tissue fibers, dental bone resorption, apical proliferation of the junctional epithelium that contributes to the appearance/presence of deep pockets between the gum and the surface of the teeth (17). These pockets contain pathogenic bacteria (anaerobic, gram-negative bacteria: *Aggregatibacter actinomycetemcomitans, Tannerella forsythensis, Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, Campylobacter rectus and Treponema denticola*) (18), which are the primary etiology of the periodontal lesion. If the pathology is not treated, this inflammatory lesion progresses, finally leading to the loss of teeth support structures with their removal (17). The periodontal disease is the result of complex interaction between pathogenic bacteria and host response, being altered by behavioral and/or systemic factors (18).

Several factors have been identified to explain the relationship between diabetes mellitus and periodontal disease: 1) impairment of immunological and inflammatory response to bacterial pathogens, 2) changes in connective tissue structure, 3) difficult healing of lesions, 4) microvascular variation, 5) development of advanced glycosylation end products (19).

The periodontal status was evaluated in 529 subjects aged ≥ 25 years who had type 2 diabetes mellitus, a glomerular filtration rate ≥ 60 mL / min / 1.73 m² and did not have macroalbuminuria (the ratio of urinary albumin: creatinine ≥ 300 mg/g). Of these patients 193 developed macroalbuminuria and 68 end stage renal disease (ESRD). Moderate and severe periodontitis predicted progression of nephropathy and ESRD in a "dose-dependent" manner in people with type 2 diabetes and no pre-existing renal disease (20, 21).

The Cochrane Collaboration reported studies that explored the relationship between glycemic control in people with diabetes and periodontal treatment (three studies included). The evidence supports the idea that improvements in glycemic control can be

anticipated following effective treatment of periodontitis. Mechanisms are not yet clear, but may refer to decreased systemic inflammation (reduced serum levels of inflammatory markers: TNF-alpha, IL-6) subsequent to the treatment and resolution of periodontitis. Large randomized trials are needed (22).

CONCLUSIONS:

After early initiation of the maximum therapeutic regimen (antibiotic therapy, double J stent and percutaneous nephrostomy), the patient presented a worsening in dynamic of the general condition, chemistry panel and imaging aspect (disorganization of the renal architecture, gas bubbles) the reason why radical nephrectomy was required. Clinical-biological post-operative evolution was good.

Periodontal disease and EPN, 2 independent pathologies, were determined by ineffective blood glucose monitoring, and EPN was the trigger factor for diabetic ketoacidosis.

Emphysematous pyelonephritis is an infection with a high degree of mortality if not identified early. For this reason, we believe that it should be discussed in diabetic patients who develop urinary tract infections with a fulminant evolution and trigger diabetic ketoacidosis. In evaluating this pathology, renal ultrasound and contrast-enhanced CT may be performed. Therapeutic options are antibiotic drug therapy, lumbar drainage and /or nephrectomy. Early identification and accurate management influence the evolution and prognosis of patients. Adjustment of glycemic values in diabetic patients result in improvement of the periodontal status.

REFERENCES

1. Huang JJ, Tseng CC. Emphysematous pyelonephritis: clinicoradiological classification, management, prognosis, and pathogenesis. Archives of internal medicine. 2000;160(6):797-805.
2. Bogdan M, Tica I, Gheorghe DN, Silosi I, Solomon S, Martu I, Surlin P, Chiscop I, Budacu C. Effect of 0.2% Chlorhexidine's Use for Treatment of Localized Gingival Lesions in Patients with Type 2 Diabetes. Rev. Chim. (Bucharest), 2016; 67(12): 2651–3.
3. Wan YL, Lee TY, Bullard MJ, Tsai CC. Acute gas-producing bacterial renal infection: correlation between imaging findings and clinical outcome. Radiology. 1996;198(2):433-8.
4. Sokhal AK, Kumar M, Purkait B, Jhanwar A, Singh K, Bansal A, et al. Emphysematous pyelonephritis: Changing trend of clinical spectrum, pathogenesis, management and outcome. Turkish journal of urology. 2017;43(2):202-9.
5. Aswathaman K, Gopalakrishnan G, Gnanaraj L, Chacko NK, Kekre NS, Devasia A. Emphysematous pyelonephritis: outcome of conservative management. Urology. 2008;71(6):1007-9.
6. Turney JH. Renal conservation for gas-forming infections. Lancet. 2000;355(9206):770-1.
7. Michaeli J, Mogle P, Perlberg S, Heiman S, Caine M. Emphysematous pyelonephritis. The Journal of urology. 1984;131(2):203-8.
8. Lu YC, Chiang BJ, Pong YH, Chen CH, Pu YS, Hsueh PR, et al. Emphysematous pyelonephritis: clinical characteristics and prognostic factors. International journal of urology : official journal of the Japanese Urological Association. 2014;21(3):277-82.
9. Solomon S, Pasarin L, Ursarescu I, Martu I, Bogdan M, Nicolaiciuc O, Ioanid N, Martu S. The effect of non-surgical therapy on C reactive protein and IL-6 serum levels in patients with periodontal disease and atherosclerosis. Int J Clin Exp Med 2016; 9(2): 4411-7.
10. Pontin AR, Barnes RD, Joffe J, Kahn D. Emphysematous pyelonephritis in diabetic patients. British journal of urology. 1995;75(1):71-4.
11. Khaira A, Gupta A, Rana DS, Gupta A, Bhalla A, Khullar D. Retrospective analysis of clinical profile prognostic factors and outcomes of 19 patients of emphysematous pyelonephritis. International urology and nephrology. 2009;41(4):959-66.
12. Falagas ME, Alexiou VG, Giannopoulou KP, Siempos, II. Risk factors for mortality in patients with emphysematous pyelonephritis: a meta-analysis. The Journal of urology. 2007;178(3 Pt 1):880-5; quiz 1129.
13. Ubee SS, McGlynn L, Fordham M. Emphysematous pyelonephritis. BJU international. 2011;107(9):1474-8.

14. Veisa G, Donciu MD, Segal L, Hurjui L, Nistor I, Ursarescu IG, Martu S**,** Burlea L, Solomon, S. Albumin as a prognostic factor for malnutrition and inflammation in chronic kidney disease. Rev. Chim. (Bucharest), 2016; 67(1): 103-105.
15. Somani BK, Nabi G, Thorpe P, Hussey J, Cook J, N'Dow J, et al. Is percutaneous drainage the new gold standard in the management of emphysematous pyelonephritis? Evidence from a systematic review. The Journal of urology. 2008;179(5):1844-9.
16. Bauman N, Sabbagh R, Hanmiah R, Kapoor A. Laparoscopic nephrectomy for emphysematous pyelonephritis. The Canadian journal of urology. 2005;12(4):2764-8.
17. Toma V, Cioloca DP, Forna D, Hurjui L, Botnariu G, Nechifor IE, Bogdan M, Costuleanu M, Simion L, Holban C. IL-18 as an important gingival inflammatory biochemical marker in children and adolescents with insulin-dependent diabetes mellitus. Rev. Chim. (Bucharest), 2016; 67(12): 2545-2551.
18. Brzezinski P, Chiriac AE, Pinteala T, Foia L, Chiriac A. Diabetic dermopathy (shin spots) and diabetic bullae (bullosis diabeticorum) at the same patient. Pak J Med Sci. 2015 31(5):1275-6.
19. Surlin P, Silosi I, Rauten AM, Cojocaru M, Foia L. Involvement of TSP1 and MMP9/NGAL in angiogenesis during orthodontic periodontal remodeling. Scientific World Journal 2014 P1-6.
20. Cioloca DP, Foia L, Holban C, Trandafirescu M, Poroch V, Maxim D, Jipu R, Costuleanu M, Toma V. Systemic diabetic context-induced biochemical periodontal alterations in children. Rev. Chim. (Bucharest), 2016; 67(12): 2409-2412.
21. Surlin P, Rauten AM, Silosi A, Foia L. Pentraxin-3 levels in gingival crevicular fluid during orthodontic tooth movement in young and adult patients. Angle Orthod. 2012. 82(5): 833-838.
22. Simpson TC, Needleman I, Wild SH, Moles DR, Mills EJ. Treatment of periodontal disease for glycaemic control in people with diabetes. The Cochrane database of systematic reviews. 2010(5):CD004714.