CASE REPORT

An ALK translocation positive carcinoma of the lung presenting as uremia due to bilateral renal obstruction

Shilo Rosenberg, MD; Ran Katz, MD; Dov Pode, MD; N. Ofer Gofrit, MD; Galina Pizov, MD; Nechushtan Hovav, MD

Department of Urology, Hadassah-Hebrew University Medical Center Jerusalem, Israel

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Abstract

We describe an unusual presentation of metastatic lung adenocarcinoma as malignant retroperitoneal fibrosis (MRPF). The diagnostic challenge, due to the small solitary lung mass and absence of a discrete retroperitoneal mass, was overcome by diagnostic laparoscopy. Molecular analysis of tissue acquired was positive for ALK gene rearrangement. Treatment of the patient with crizotinib *reversed* MRPF. He was weaned off the nephrostomy tubes and is with stable renal function 11 months after diagnosis.

Introduction

Malignant retroperitoneal fibrosis (MRPF) is usually the end result of a known disseminated neoplastic process. These patients usually have one or both upper tracts permanently drained by either ureteral stents or nephrostomy tubes and, as a result, are prone to infections, bothersome symptoms that further decrease their quality of life and the need for recurrent invasive procedures. With better understanding of tumour biology, in an era of targeted therapy, the natural history of some patients with MRPF can be improved.

Case report

A 48-year-old non-smoking male presented to the emergency room complaining of general weakness, weight loss and lower abdominal discomfort that had progressed over 3 months. He had no significant medical history. On arrival, vital signs were within normal limits and physical examination of the head, neck and chest showed no abnormality. The abdomen was soft with no signs of hepatosplenomegaly or peritoneal irritation. The genitalia showed no pathology and the prostate was small, smooth and symmetric with no signs of blood per rectum. Laboratory values for white blood count, hemoglobin and creatinine levels were 13.2×10^{9} /L, 13.2 gr% and 280 µmol/L, respectively. Urinalysis was normal and blood gases obtained were within normal range. Ultrasound of the abdomen and pelvis demonstrated bilateral hydronephrosis and minute amount of free fluid in the pelvis; other organs examined were unremarkable. A noncontrast computer tomography (CT) of the abdomen and pelvis displayed bilateral hydroureteronephrosis up to the level of the sacroiliac joint. No cause for obstruction was found. A 19-mm spiculated lesion was detected at the base of the right lung (Fig. 1).

Cystoscopy and bilateral retrograde pyelography demonstrated a normal urinary bladder, but bilateral obstructed distal ureters. The right distal ureter had a "corkscrew" appearance (Fig. 2a) and the left distal ureter had a piliform appearance (Fig. 2b).

Bilateral ureteral stents (c-flex, 6.0F, 26 cm, Cook Medical, Bloomington, IN) were inserted without difficulty. In the following days, postobstructive diuresis occurred with normalization of creatinine levels. Subsequently, a CT of the chest, abdomen and pelvis with oral and intravenous contrast was done. No additional lung lesions were seen. Discrete density increase of the retroperitoneal fat around the ureters, at the level of the sacrum was detected, as well as free fluid in the pelvis (Fig. 3).

No abdominal or retroperitoneal lymph nodes or discrete masses were detected. He was discharged, but readmitted 10 days later due to oliguria and recurrent renal failure. Bilateral antegrade pyelography displayed complete ureteral obstruction at the level of the sacrum (Fig. 4).

Bilateral nephrostomies were inserted and the ureteral stents removed. Normal creatinine levels were reached within 3 days. Tumour marker levels obtained upon admittance, including CEA (normal below 3 ng/mL), CA-125 (normal below 35 ng/mL), CA19-9 and prostate-specific antigen (normal below 4 ng/mL), were 39.77 ng/mL, 849 ng/mL, 10.14 u/mL and 1.26 ng/mL, respectively. Subsequent colonoscopy and gastroscopy carried out were normal. A right lung biopsy showed primary adenocarcinoma of the lung



Fig. 1. A 19-mm spiculated lesion detected at the base of the right lung.

(Fig. 5a) and stained positive for TTF-1 (Fig. 5b) and CK-7 (Fig. 5c), but negative for CK-20.

At this stage, we consulted with the oncologist. The differential diagnosis included primary lung adenocarcinoma with extrathoracic manifestations or two unrelated disease processes. In the absence of a discrete retroperitoneal mass, we decided to proceed with transperitoneal diagnostic laparoscopy. At laparoscopy, the peritoneum was seeded with multiple small white grayish implants. Serous coloured fluid was found in the pelvis and sent for cytology. Three peritoneal implants were resected and sent for pathologic evaluation. Cytology was positive for carcinoma cells. The peritoneal biopsies stained positive for TTF-1 and CK-7 and were compatible with poorly differentiated adenocarcinoma of the lung. Hematoxilin and eosin staining of these biopsies displayed islands of adenocarcinoma with signet ring cells surrounded by a desmoplastic reaction (Fig. 6).

A diagnosis of stage IV non-small cell lung cancer (NSCLC) was made. Molecular analysis, by fluorescence in situ hybridization (FISH) assay, of peritoneal lesions was positive for ALK gene rearrangement and negative for EFGR gene mutation. The patient was perscribed crizotinib 250 mg twice daily. Six weeks after the crizotinib treatment, a repeat nephrostogram showed unobstructed uereters (Fig. 7). Tumour markers CEA and CA-125 levels decreased to 1.66 ng/mL and 8.0 ng/mL, respectively.

The nephrostomies were closed and later removed. Serial blood creatinine levels taken over a period of 11 months were within the normal range. A CT of the chest performed 2 months after the initiation of crizotinib treatment demonstrated shrinkage of the lung lesion to a size of 10 mm. The lung lesion remained stable in size on subsequent chest CT done 11 months later (Fig. 8).



Fig. 2a. The right distal ureter had a "corkscrew" appearance.

Discussion

Ureteral obstruction due to neoplasia is caused by direct extension of a pelvic tumour, retroperitoneal lymphadenopathy or MRPF. Adenocarcinomas of the stomach, lung, colon, pancreas and breast, in addition to lymphoma, sarcoma and carcinoids, have been repeatedly mentioned as causes of MRPF.¹ The incidence of ureteral involvement in neoplasia is 0.2%.² The phenomenon of MRPF is due to the ability of scirrhous tumours, such as adenocarcinomas, to produce an extracellular desmoplastic reaction.³ The increase in soft tissue density around the ureters on CT, the ureteral



Fig. 2b. The left distal ureter had a piliform appearance.

appearance on retrograde pyelography and the desmoplastic reaction seen on the histologic sections taken from the peritoneal implants suggest that distal bilateral ureteral obstruction in our patient was the result of MRFP. In previous reports lung adenocarcinomas causing hydronephrosis was due to lymphadenopathy or a discrete retroperitoneal mass.^{4,5} In these reports, hydronephrosis was unilateral needing no immediate upper tract drainage and ALK status was not determined. To our knowledge, this is the first case of ALK-positive NSCLC with bilateral hydronephrosis as a result of MRPF. In the absence of a discrete abdominal mass, elevated CEA and presence of a normal colonoscopy and gastroscopy, we faced a diagnostic challenge posed by the unique clinical presentation of this patient. MRPF is charac-



Fig. 3. In the pelvis, at the level of the sacrum, discrete density increase of the retroperitoneal fat around the ureters, as well as free fluid in the pelvis, was seen.



Fig. 4. Bilateral antegrade pyelography displayed complete ureteral obstruction at the level of the sacrum.

terized histologically by metastatic cells dispersed diffusely in the fibrotic plaque. CT-guided fine needle aspiration or core biopsies are far less effective than deep surgical biop-



Fig. 5a. A right lung biopsy showed primary adenocarcinoma of the lung.

sies, in attaining adequate tissue for diagnosis.⁶ To proceed with the diagnostic effort, we chose diagnostic laparoscopy. The 2 main advantages of diagnostic laparoscopy are the possibility of detecting lesions that evade the resolution of standard abdominal CT and the possibility of acquiring tissue for molecular analysis. In an era of expanding use of targeted therapy in oncology, the acquisition of tissue for molecular analysis is of cardinal importance.

In cases of external compression of the ureters, as in this case, draining the upper tracts by ureteral stents should be done with caution as they often give a false sense of security. In cases of retroperitoneal fibrosis drained by ureteral stents, patients should be continuously monitored with serial creatinine levels and upper tracts imaging.

Lung cancer in never smokers (LCINS) is a recently accepted entity. It carries unique histologic features, oncogenic patterns and most patients are diagnosed at stage



Fig. 5c. A right lung biopsy negative for CK-20.



Fig. 5b. A right lung biopsy stained positive for TTF-1.

IV. Adenocarcinoma is the most common tumour. The most prevalent oncogenic alterations include the epidermal growth factor receptor mutations, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations, anaplastic lymphoma kinase rearrangement (ALK-EML4) and KIF5B-RET translocations.^{7,8} Our patient is a young male non-smoker, with adenocarcinoma signet ring type. These features concur with other reports of ALK positive NSCLC patients.9 Crizotinib was authorized by the FDA, even before the results of the pivotal phase 3 trial comparing this drug to chemotherapy were available, due to its ability to induce an impressive response rate and progression-free survival in patients harbouring the ALK translocation. Indeed in the phase 2 trial, there was some clinical response in nearly all patients to treatment and RECIST (Response Evaluation Criteria In Solid Tumors) verified objective response rates



Fig. 6. Hematoxilin and eosin staining of these biopsies displayed islands of adenocarcinoma with signet ring cells surrounded by a desmoplastic reaction.



Fig. 7. Six weeks after the crizotinib treatment, a repeat nephrostogram showed unobstructed uereters.

of around 60%.¹⁰ Despite the marked antitumour activity of crizotinib, ALK driven cancers invariably become resistant to crizotinib. Resistance develops on average within a year or two of tyrosine kinase inhibitor (TKI) therapy.¹¹ Patients presenting with MRPF are often thought of having a "one way ticket" in terms of morbidity and mortality; however, with better understanding of tumour biology and the development of novel drugs this is changing. In our case, 6 weeks after crizotinib therapy, bilateral nephrostograms showed no ureteral obstruction and the nephrostomy tubes were removed. A chest CT at 8 weeks showed the solitary lung lesion had shrunk by 45%. The effect of the drug is still evident 11 months into therapy. The use of biomarkers in NSCLC is controversial.¹² In an era of tailored treatment for advanced NSCLC with specific histology, the use of biomarkers may show prognostic value. In our case, CEA and CA-125 values were elevated before but normalized 6 weeks into crizotinib treatment.

Conclusion

We report an unusual case of stage IV, ALK positive NSCLC presenting initially as renal failure with bilateral distal ureteral obstruction due to MRPF. When drained by ureteral stents, these patients should be regularly monitored. In rare cases when MRPF is the initial presentation of an oncologic disease, in the absence of a discrete mass, laparoscopy is very important in the diagnostic effort. This case report underscores the importance of tumour genotyping in LCINS patients due to their unique tumour biology and the rapid effectiveness of the



Fig. 8. A computed tomography of the chest performed 6 months after the initiation of crizotinib treatment demonstrated shrinkage of the lung lesion to 10 mm.

new generation tyrosine kinase inhibitors. Treating the patient with crizotinib reversed ureteral obstruction within a short period of time allowing him to be weaned off the nephrostomy tubes; this greatly improved his quality of life.

Competing interests: None declared.

This paper has been peer-reviewed.

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Correspondence: Dr. Shilo Rosenberg, Urology Department, Hadassah Medical Center; shilo890@gmail.com