Urosepsis Due to Fluoroquinolone-Resistant Escherichia coli After Ultrasonographic-Guided Transrectal Implantation of Fiducial Markers

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Introduction

Escherichia coli (E coli) is the most common pathogen of infectious complications surrounding transrectal procedures of the prostate. The widespread practice of administering fluoroquinolone antimicrobial prophylaxis prior to such procedures has reduced the rate of periprocedural infections, yet the incidence of fluoroquinolone-resistant E coli remains, which has spurred investigations into preventive measures. The administration of preprocedural enemas to mechanically reduce bacterial count within the rectal vault has failed to improve outcomes. However, studies have identified recent antibiotic use and international travel as pertinent risk factors for the development of fluoroquinolone-resistant infection. Further, these resistant strains of E coli have often been found to exhibit resistance to other commonly prescribed medications for urinary tract infections (UTIs) and necessitate the administration of broad-spectrum cephalosporins, broad-spectrum penicillins, or carbapenems when a serious infection, such as urosepsis, is suspected.

Case Report

A man aged 57 years was diagnosed with Gleason grade 3+4 adenocarcinoma of the prostate involving 10% to 25% of the tissue within 2 of 12 total biopsy cores. Initial digital rectal examination (DRE) identified a benign gland without nodularity. Thus, the tumor was clinically staged as T1cNxMx according to the 2010 American Joint Commission on Cancer guidelines and deemed to be an intermediate risk with regard to recurrence as defined by the National Comprehensive Cancer Network and the American Urologic Association (AUA). Treatment options, including radical prostatectomy, external beam radiation therapy, and interstitial brachytherapy, were discussed with the patient in detail.

After he opted for external beam radiation therapy, the patient agreed to a treatment protocol inclusive of intensity-modulated radiation therapy (IMRT) and the prerequisite placement of gold fiducial markers. Thus, 3 months following prostatic biopsy, he was given an oral dose of 500 mg of levofloxacin prior to the transrectal ultrasound (TRUS)-guided placement of four gold fiducial markers within the prostate gland. He also received levofloxacin 500 mg daily by mouth for two days after the procedure. Two days following the placement of fiducial markers, he returned to our facility complaining of fever, nausea, and vomiting. He was also experiencing perineal discomfort, awakening chills, and malaise. He denied difficulty with voiding.

On physical examination, the patient was febrile (101.8° F), exhibited regular tachycardia (125 beats per minute), was normotensive (140/78 mmHg), and was without tachypnea (20 breaths per minute). His abdomen was benign and the bladder was not palpable. No costovertebral angle tenderness was present. A gentle DRE demonstrated a firm, nontender prostate without masses. There was no gross blood in the rectal vault.

Serological evaluation noted a slight leukocytosis (12,500 k/μL) with the differential noting a left shift. The patient was not anemic (16.6 g/dL), and he was slightly thrombocytopenic (86 k/μL). Urinalysis displayed yellow urine with a high specific gravity (1.080) consistent with dehydration, a normal pH (6.0), trace protein (30 mg/dL), negative nitrates, large leukocyte esterase, pyuria (51-100 white blood cells/high-powered field), and trace bacteria consistent with an infectious process, and microscopic hematuria.

The DRE was inconsistent with acute bacterial prostatitis. However, UTI, potentially complicated by...
bacteremia, was suspected, so initial doses of levofloxacin, vancomycin, and fluconazole were administered to the patient as empirical antibiotic coverage in the emergency department. On admission, intravenous levofloxacin 500 mg daily, piperacillin/tazobactam 4.6 g every 6 hours, and vancomycin 1 g 3 times daily were administered. By hospital day 2, the urine and blood cultures demonstrated Gram-negative rods, so the vancomycin was discontinued. The final culture and sensitivities identified the pathogen as E coli sensitive to piperacillin/tazobactam and trimethoprim/sulfamethoxazole but resistant to both levofloxacin and ciprofloxacin. Therefore, only the piperacillin/tazobactam was continued. The patient’s fever defervesced, repeated blood and urine cultures were negative, and he was discharged home on oral trimethoprim/sulfamethoxazole: 2 double-strength tablets twice daily for 10 days to complete a 14-day course of culture-specific antibiotics appropriate for a Gram-negative bacteremia and complex UTI. The final diagnosis was UTI associated with urosepsis due to fluoroquinolone-resistant E coli.

Discussion

Recently, the delivery of radiation therapy has been refined to tailor radiation fields to each patient and to allow for the administration of escalated radiation doses to targeted sites (eg, the prostate) while reducing unnecessary exposure of adjacent organs. Dose escalation improves the efficacy and accuracy of radiation therapy, thereby limiting adverse events to adjacent organs such as the bladder and rectum. Of those techniques, concomitant utilization of fiducial marker placement and IMRT has allowed the radiation oncologist to adjust for real-time prostate motion during therapy, which typically involves 1 to 5 minutes of daily treatment 5 days per week over the course of 4 to 8 weeks. Increasingly, studies support this technique as a simple, safe, and appropriate therapy. However, complications have been reported and include urosepsis. Despite the risk of such severe infectious complications, common minor infectious complications include fever (1.9%), UTI (3.2%), and prostatitis (1.6%). A report of infectious complications following TRUS-guided prostatic biopsies, performed in a similar setting and manner as TRUS-guided placement of fiducial markers, identified the rate of post-procedural sepsis due to fluoroquinolone-resistant E coli as ranging from 0.1% to 0.9%. It has also been noted that antibiotic prophylaxis significantly lessens the rate of periprocedural infections affiliated with TRUS-guided prostatic biopsies. The AUA endorses the use of fluoroquinolone prophylaxis for up to 24 hours surrounding transrectal procedures involving the prostate, and 90.1% of urologists within the United States are following this practice. Sepsis is a rare complication after intraprostate fiducial marker implantation. In a study of 1,021 patients who underwent intraprostatic fiducial marker implantation, only 1 developed UTI and sepsis despite broad antibiotic prophylaxis with levofloxacin and nitrofurantoin. Our patient exhibited urosepsis secondary to a fluoroquinolone-resistant E coli strain 2 days after the TRUS-guided placement of intraprostatic fiducial markers, at which time a fluoroquinolone (levofloxacin) had been administered. In accordance with the AUA best practice guideline for prophylactic antibiotic administration, a fluoroquinolone would be the antimicrobial of choice prior to a TRUS-guided prostate biopsy. As fiducial markers are inserted in a similar fashion in which TRUS-guided biopsy of the prostate is performed, and since there is a paucity of data regarding infectious complications specifically related to fiducial marker placement, it could be assumed that urologists employ similar antimicrobial prophylaxis strategies prior to the execution of the TRUS-guided placement of fiducial markers.

Fluoroquinolones are potent, penetrate prostatic tissue well, are orally administered, and have long-lasting urinary bactericidal activity against both Gram-positive and Gram-negative bacteria. Urologists frequently use these antibiotics in prostate-related procedures, including the intraprostatic placement of fiducial markers. This practice is consistent with the 2011 guidelines of the European Association of Urology, which recommend fluoroquinolones — with ciprofloxacin superior to ofloxacin — for the prophylactic antibiotic used for prostate biopsy and is supported by the AUA, which offers the alternate regimen using a second- or third-generation cephalosporin. If the patient has been allergic to penicillin, a combination of an aminoglycoside and metronidazole or clindamycin is appropriate. With the widespread adoption of periprocedural fluoroquinolone administration, it is important to note that there are many studies describing the rising incidence of fluoroquinolone-resistant E coli sepsis. A retrospective review of 1,273 patients undergoing TRUS-guided prostate biopsy with levofloxacin or gatifloxacin prophylaxis demonstrated a 2.4% rate of infectious symptoms after biopsy, 50% of which were secondary to fluoroquinolone-resistant microbes. In that same cohort, of those Gram-negative bacilli that were resistant to fluoroquinolones, 44% were also resistant to trimethoprim/sulfamethoxazole. However, 100% of these resistant bacterial strains were susceptible to ceftriaxone, cefotaxime, cefotetan, and cefotetan. These findings are substantiated by another recent retrospective trial that implicated E coli as the most common pathogen of prostatitis after TRUS-guided prostate biopsy, followed by Klebsiella pneumonia and Staphylococcus epidermidis. Of the...
isolated Gram-negative organisms that were implicated, 85.7% were resistant to fluoroquinolone but were highly sensitive to third-generation cephalosporins such as ceftriaxone (85.7%) and were 100% susceptible to the carbapenems imipenem and meropenem. This supports the assertion by Zaytoun et al\(^5\) that posttransrectal prostate procedure infections should be managed with broad-spectrum cephalosporins.

To prevent infectious complications, the utilization of enemas to mechanically reduce the bacterial content of the rectal vault has been investigated. However, the work of Mosharafa et al\(^6\) did not demonstrate a significant difference in postprocedural complications between those who received a preprocedural enema and those who did not \((P = .061)\). Prior use of a fluoroquinolone within 6 months before the procedure was a significant finding in this study, resulting in a 3.8 times higher risk of the development of acute prostatitis after TRUS-guided prostate biopsy \((P = .042)\). This finding was not isolated.\(^7\)\(^,\)\(^2\)\(^2\) Further, Patel et al\(^8\) also identified recent travel — specifically overseas — as a risk factor for the development of infections due to fluoroquinolone-resistant \textit{E coli}.

Another proposal to reduce infectious complications is the utilization of targeted antibiotic prophylaxis. Although it is standard practice to defer transrectal instrumentation of the prostate until an individual demonstrates sterile urine, some researchers are now investigating the use of a preprocedural rectal swab, particularly in patients at risk for harboring fluoroquinolone-resistant microbes, which has demonstrated the presence of these microbes in 22% of all patients infected.\(^2\)\(^2\) If the culture is positive, then an alternative nonquinolone antibiotic can be prescribed for antimicrobial prophylaxis; a practice now applied at the Moffitt Cancer Center.

**Conclusions**

We reported on a rare case of sepsis after transrectal ultrasound (TRUS)-guided placement of gold fiducial markers within the prostate when preparing a patient for intensity-modulated radiation therapy. Despite a lack of specific guidelines with respect to antibiotic prophylaxis prior to TRUS-guided placement of fiducial markers within the prostate, guidelines specific to transrectal prostate biopsy are applicable due to the inherent similarities between both procedures. Antibiotic prophylaxis using a fluoroquinolone or second- or third-generation cephalosporin remains a mainstay of transrectal prostate manipulation, allowing for an acceptably low rate of infectious complications. However, there should be an increased suspicion of fluoroquinolone-resistant microbes in the setting of fiducial marker placement, which is often performed in subsequent close chronological proximity to TRUS-guided prostate biopsies. At this time, antimicrobial prophylaxis is generally administered using a fluoroquinolone. If fevers, chills, tachycardia, and/or hypotension are present following the TRUS-guided placement of fiducial markers within the prostate, empirical treatment should cover fluoroquinolone-resistant microbes and include a broad-spectrum cephalosporin, carbapenem, or broad-spectrum penicillin, with or without an aminoglycoside. Future preprocedure selection of antibiotic prophylaxis may be guided by a culture or rapid-detection systems that can be used to rule out the presence of a fluoroquinolone-resistant organism within the rectum and should take into account a patient’s recent receipt of antimicrobials.

**References**

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