TESTICULAR AND ABDOMINAL ULTRASOUND IMAGING IN PSEUDOXANTHOMA ELASTICUM

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INTRODUCTION

Pseudoxanthoma elasticum is a rare genetic disorder that results in mineralization of dystrophic elastic fibers of the dermis, Bruch's membrane of the choroid, and middle-sized arteries[1]. The disorder is due to a mutation in the gene that encodes the membrane transport protein ABCC6/MRP6[2]. It is thought to be an autosomal recessive disorder, although mild manifestations have been described in carriers[3], and mild ultrastructural changes suggestive of PXE have been found in clinically unaffected carriers[4]. Complications of PXE include central vision loss, premature arterial occlusive and coronary disease, and acute upper gastrointestinal bleeding[1]. Anecdotal series of abdominal ultrasound imaging comprising five cases have shown hyperechoic foci in the renal parenchyma, pancreas, and spleen[5-8], although it has been suggested that such findings are not specific for PXE[8]. We have recently examined testicular sonograms in two 13-year old males which showed striking features of testicular microlithiasis.

Testicular microlithiasis (TM) presents as multiple bilateral randomly distributed small (<2 mm) hyperechoic foci in the testicular parenchyma[9]. Testicular microlithiasis is thought to be due to deposits in the seminiferous tubules consisting of a central calcified core surrounded by concentric lamellae of collagen and proteoglycans[10]. It was initially described in association with testicular tumors[11] and subsequent series showed it to be associated with either subsequent development of testicular malignancy or intraepithelial neoplasia[12]. TM has also been described in association with cryptorchid testes, Klinefelter syndrome, Down syndrome, infertility, subfertility, hypogonadism, and pulmonary microlithiasis[12]. A prospective study[13] of 1504 young military personnel showed an incidence of 5.6% (ranging from 4% in Caucasians to 15.6% in African-American men). None had testicular neoplasms suggesting that this may be a more common finding in asymptomatic men than was previously realized. A study of 2215 testicular sonograms in a referred population at a British hospital[14] showed an incidence of TM of 1.4% with an incidence of testicular tumors of 15% (versus 1.1% of those without TM, a relative risk (RR) of about 14). Another British study of a referred population of 4819 patients[15] showed an incidence of TM of 0.68% and RR of concurrent testicular tumor of 21.6). A recently published study[16] of 1079 consecutive testicular sonograms showed classic TM (>5 microliths in both testes) in 3.7% of patients and 14.4% had limited TM. Eight percent of patients with classical TM had testicular tumors, while 5.8% of those with limited TM had testicular neoplasms. Although the majority of patients with testicular tumors had coexistent TM, in this study over 90% of patients with TM did not have a tumor at the time of scanning. It is currently recommended that patients with TM receive follow-up sonograms and urologic examination to watch for tumors[17], although the author of the study on TM in healthy military personnel has questioned the necessity for this[13].

Since the finding of TM in PXE has not been described in the literature and since it has been found in two consecutive individuals with PXE, we propose to do a study to determine the frequency of TM in PXE. If it is indeed a frequent finding in this disorder (which is known to be associated with the presence of hyperechoic areas suggesting calcification in other organs), then it is much less likely to be associated with testicular tumors in this population, and this information will be of immense value to radiologists and

urologists in counseling and following patients with TM and PXE, sparing the patients unnecessary anxiety. Since carriers of the PXE mutation may have limited manifestations of PXE[3], we will examine some obligate carriers if TM is found with high frequency in PXE.

SUBJECTS AND METHODS

Participants will be recruited from the data base of PXE International, Inc. PXE International is a non-profit lay advocacy and support group for those with PXE and is based in Washington, DC. Sharon Terry will recruit participants, from throughout New England in the same manner as for other studies conducted with the collaboration of PXE International. To be included in the study, participants must have confirmed PXE (accepted criteria include typical skin lesions in flexural areas, a diagnostic biopsy in lesional skin, and the presence of angioid streaks, although the presence of angioid streaks and typical skin lesions with a positive family history would be acceptable, as would a positive biopsy of non-lesional skin in the absence of diagnostic skin lesions in an individual with angioid streaks). If TM is found frequently in the sample of participants who are affected with PXE, we will also test some unaffected carriers. A carrier would be considered an individual who is found to carry the PXE mutation in one allele on mutational screening (currently considered a research test conducted by PXE International) or the parent or offspring of an affected individual. An informed decision making process leading to a signed written informed consent would be required of all participants and minors would be required to sign an assent form. Testicular sonograms will be done at the Department of Diagnostic Imaging at Rhode Island Hospital and all images would be stored there. Images will be reviewed for the presence or absence of TM and any other sonographic findings. Our goal is to examine 20 patients with PXE. This is a rare disorder, with an estimated incidence of about 1:50,000, and about 2/3 of those affected are female (the reason for the gender discrepancy being unknown), so this goal is ambitious but attainable.

Participants will be administered a short questionnaire to ascertain the presence or absence of symptoms of testicular or urologic disease. A urologist or urology resident will examine the testes at the time of the ultrasound examination.

We will also examine testicular sonograms done at other institutions on patients with PXE that will be obtained through PXE International. We will also make an effort to track down testicular pathology specimens from surgical pathology and autopsy files at Rhode Island Hospital and worldwide to better understand the mechanism and histopathology of TM in this disorder.

We will not give participants results, except in a general manner at the conclusion of the study. However, if any information is gained that has implications for the healthcare of a participant, that information will be conveyed to the participant in a timely manner by one of the medically qualified investigators with suggestions for appropriate follow-up care.

ANALYSIS OF DATA

The incidence of TM in PXE will be compared to that in consecutive aged matched testicular sonograms in the files of the Department of Diagnostic imaging as well as the incidence in previously published studies. We do not plan to test a control group at this time because the incidence of TM is so low in the normal population that a meaningful control group would have to be quite large.

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