

Is magnetic resonance imaging helpful in detecting significant prostate cancer in patients with haematospermia, normal prostate specific antigen level and digital rectal examination. A single institution, observational, and retrospective study in a United Kingdom hospital

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Introduction Haematospermia is an uncommon clinical condition that may be associated with prostate cancer. The optimal investigation of haematospermia is unknown. The aim of this study was to investigate haematospermia as a presenting symptom of significant pathology and to assess the diagnostic value of magnetic resonance imaging (MRI).

Material and methods Patient and treatment parameters were collected from a practice cohort of men referred to a urology center presenting with haematospermia. We used a multivariate logistic regression model to test the independent significance of MRI in detecting prostate cancer (PCa) after adjusting for other known predictors of PCa detection.

Results A total of 125 men (median age 58 years) were evaluated between 2012–2015. In the univariate and multivariate logistic regression model MRI was a significant predictor of PCa diagnosis after adjusting for age, prostate specific antigen (PSA) and digital rectal examination (DRE) results (Odds Ratio (OR) 14.15, $p = 0.001$). Of 107 patients who underwent MRI prostate imaging, 31 (28.9%) had reports suspicious of PCa. In 26 patients, other benign conditions were detected on MRI. PCa was detected in 12 (25.5%) of the 47 men (median age 61 years; range 43 to 85) who underwent prostate biopsies. Eight (17%) of these patients had Gleason ≥ 7 grade cancer. The persistence of haematospermia was not an independent predictor of cancer diagnosis (OR 0.20, $p = 0.15$).

Conclusions PCa is not commonly associated with haematospermia. MRI seems to be improving detection rate of a significant PCa, particularly in patients presenting with haematospermia and normal PSA levels and DRE examination. Duration of haematospermia does not predict the presence of PCa.

Key Words: cancer <> magnetic resonance imaging <> prostate <> investigations <> haematospermia

INTRODUCTION

Haematospermia is defined as the presence of blood in the semen. It was first documented centuries ago

by physicians from Hippocrates, Paré, Morgagni, Galen to Fournier [1]. Although considered to be a rare, benign, and self-limiting symptom in most cases, it may cause significant anxiety to the patient.

As a result, urologists often receive specialist referrals from primary care in men of all ages, accounting for around 1% of all referrals. Its prevalence has been reported as 0.5% of a prostate cancer screening population [2]. In the past, its significance generally has been attributed to benign conditions such as inflammatory, infective or idiopathic changes [3, 4, 5]. However, more recently Han et al. proposed an association of haemospermia with prostate cancer. In a large prostate specific antigen (PSA) screened population of 26 126 men, he reported an increased incidence of haemospermia (13.7%) in men subsequently diagnosed with prostate cancer than those who did not have haemospermia (6.5%: Odds Ratio (OR) 1.73 $p = 0.054$) [2]. As the understanding of haemospermia evolved and more evidence of association with potential malignancy emerged, the consensus on investigative modalities also changed [6]. Previously urologists usually recommended conservative management, such as antibiotic therapy and reassurance for this condition. Recently a more structured approach has been proposed. Ng et al. suggested investigating patients with PSA and digital rectal examination (DRE) only over the age of 40, finding that other modalities such as flexible cystoscopy, ultrasound or intravenous urography (IVU) had very poor diagnostic yield [7]. Furthermore, transrectal ultrasound, prostate biopsy and magnetic resonance imaging (MRI) have been proposed in the over 40-age group by other investigators [6, 8]. Although costly, a MRI can provide important etiological information for patients with haemospermia and with modern, high resolution scans, causes of haemospermia could be elucidated. However, the evidence basis for the investigation of choice and its predictive value of detecting significant pathology remains elusive.

In the current study, we aimed to investigate haemospermia as a presenting symptom and to assess the diagnostic value of MRI. To our knowledge this represents the largest reported case series of haemospermia investigated by MRI.

MATERIAL AND METHODS

Consecutive patients presenting to our clinic with haemospermia between January 2012 and February 2015 were included in this study. Most of the patients presented with a single episode or an episode that had lasted only a few weeks. For the purposes of this study persistent haemospermia was defined as ≥ 4 episodes or lasting longer than 6 months. Data on patient age, concurrent presenting symptoms, and urological history were retrospectively collected. In addition, patient investigations and final diag-

noses were recorded. PSA and DRE findings were noted in the over 40-age group. A 12-core standard transrectal ultrasound (TRUS)-guided prostate biopsy was carried out when patients had an elevated PSA and/or abnormal DRE and/or abnormal MRI or strong family history of prostate cancer.

Magnetic resonance imaging examinations were performed with a 1.5 T clinical scanner (Siemens, Germany) with patients in the supine position. The scanning sequences included SE T1-weighted images and T2-weighted images. All patients underwent enhanced scanning with gadolinium (GD-DTPA). The scanning parameters were as follows: T1WI TR/TE = 550 ms/12 ms, T2WI TR/TE = 4000 ms/97 ms, slice thickness of 3.0–8.0 mm and a between-slice interval of 0.8–0.9 mm. The matrix sizes were 320 9 220 (sagittal view), 320 9 256 (axial view) and 320 9 256 (coronal view). In contrast to current recommendations, other modalities, which are considered a part of multiparametric MRI (dynamic contrast enhanced imaging, and magnetic resonance spectroscopic imaging) were not examined. At the time of the study the prostate imaging reporting and data system (PIRADS) had not been introduced in our hospital and therefore only two categories of reporting were used (normal vs. suspicious), where any suspicious scan would include PIRADS ≥ 3 .

Statistical analysis

Initial serum PSA was analyzed as a continuous variable. The initial DRE result was categorized as suspicious vs. non-suspicious for cancer. The Fisher's Exact test was performed to study the relationship between haemospermia and MRI results categorized as normal vs. suspicious. Subsequently, univariate and multivariate logistic regression analyses were performed using potential predictors of subsequent prostate cancer diagnosis. All statistical analyses were performed using commercially available SPSS Statistics software (IBM United Kingdom Limited, Portsmouth).

RESULTS

A total of 125 men were evaluated between January 2012 and March 2015. The age range of the patients was 21–85 years (median age 58 years). There were 15 patients <40 years of age and 110 patients ≥ 40 years of age. Haemospermia among patients lasted between 6 and 120 months (mean duration = 12.9 months). In most patients, haemospermia was not associated with any other symptoms. In a few patients, haemospermia was accompanied by hematuria, discomfort in the perineal region, a decrease

in orgasmic intensity, dysuria, ejaculatory pain, frequency or urgency. The latter three symptoms were present in patients younger than 40 years, which may suggest inflammatory and/or infective pathologies in this group. Unfortunately, we had no information available on sexually transmitted diseases in our cohort of patients.

In the univariate and multivariate logistic regression model, MRI when documented as suspicious (PIRADS ≥ 3), was a significant predictor of prostate cancer diagnosis on biopsy after adjusting for age, PSA and DRE results (OR 14.15, $p = 0.001$) (see Table 3). Of 107 patients who underwent MRI prostate imaging, 31 (28.9%) had reports suspicious of prostate cancer. Eighteen patients of 125 had not had MRI performed due to various contraindications. Prostate cancer was detected in 12 (25.5%) of the 47 men (median age 61 years; range 43 to 85) who underwent prostate biopsies. Eight (17%) of these patients had Gleason ≥ 7 grade cancer. The persistence of haemospermia was not an independent predictor of cancer diagnosis (OR 0.20, $p = 0.15$). In 26 patients, other benign conditions were detected on MRI (see Table 1). There were 14 MRI reports suggesting inflammation of the prostate and/or seminal vesicles (SV). Five of these 14 patients were above 40 years of age with 4 patients who had confirmed inflammation on histological sample. All of the prostate cancer diagnoses were above the age of 40.

DISCUSSION

Haemospermia often causes anxiety and distress in sexually active men due to the possibility of a malignant disease. However, it is thought to be a generally painless, benign and self-limiting symptom [9]. Thus, the main purpose of diagnosing the cause of haemospermia is the exclusion of malignancy and reassuring the patient and his partner.

As identified by previous studies, the commonest causes of haemospermia are infection or inflammation of the urogenital tract, obstruction or cysts of seminal vesicles, iatrogenic trauma, vascular anomalies of the posterior urethra and neoplasms [9].

Traditionally, the investigations for haemospermia depended mainly on medical history and physical examination and included semen analysis, transrectal ultrasound examination (TRUS) and occasionally vaso-seminal vesiculography.

It has been suggested that TRUS should be considered the first choice for imaging examination in cases of haemospermia [10] and should be performed in patients over 40 years of age with symptomatic or recurrent haemospermia [9, 11] due its safety,

low cost and effectiveness. However, TRUS as a diagnostic imaging modality is characterized by several important disadvantages. Due to TRUS's low resolution of pelvic spatial structures, inter observer variability grossly dependent on operator's basic theoretical knowledge of the detailed anatomic structure and the embryonic development of the male urogenital tract, it often produces incorrect etiological diagnosis of haemospermia. Some authors

Table 1. Characteristics of other than prostate cancer abnormalities detected by magnetic resonance imaging (MRI)

Performance of MRI imaging	Number of patients
Cysts in epididymal area	9
The signal intensity changed in seminal vesicles (SV) – haemorrhage	13
Dilatation of SV (widths >1.7 cm)	4

Table 2. Characteristics of men with prostate cancer in screened population in the study by Han et al. compared to our haemospermia and prostate cancer (PCa) population

	Number of PCa (%) with no haemospermia in Han et al. study	Number of PCa + haemospermia (%) in our study
Age:		
Younger than 51	17 (1.0)	0 (0)
51–60	403 (23.6)	2 (16.7)
61–70	767 (44.9)	8 (66.6)
Older than 70	521 (30.5)	2 (16.7)
Initial screening prostate specific antigen (ng/ml):		
0–2.5	590 (34.9)	3 (25)
2.6–4.0	351 (20.7)	2 (16.7)
4.1–10.0	561 (33.2)	4 (33.4)
10.1–20.0	130 (7.7)	2 (16.7)
Greater than 20	60 (3.6)	1 (8.2)
Total number of PCa	1692 (100)	12 (100)
Digital rectal examination:		
Suspicious for PCa	435 (25.5)	6 (50)
Non-suspicious	1,273 (74.5)	6 (50)
Totals	1,708 (100)	12 (100)

Table 3. Result of multivariate logistic regression model predicting prostate cancer detection outcome. Where for magnetic resonance imaging (MRI), only two categories of reporting were used (normal vs. suspicious)

	OR	p Value	95% confidence interval (CI)
MRI	14.15	0.001	2.65–16.12
Age	1.55	<0.001	1.29–1.89
Prostate specific antigen	3.17	<0.001	2.56–3.78

OR – odds ratio

reported that TRUS has a false-positive rate of 50% and therefore it should not represent a definitive but rather a screening modality of haematospermia patients [6, 12].

To overcome problems associated with ultrasound, magnetic resonance imaging has been introduced as the investigation of choice. It has been considered the gold standard for imaging the accessory sex glands and their ducts [6] and more frequently used for evaluating patients with persistent haematospermia when initial examinations fail to clarify the causative lesions [13, 14]. It has been proposed to perform an MRI when transrectal ultrasonography is not satisfactory, is inconclusive or when the results are in doubt [15, 16].

We studied the diagnostic value of MRI in patients who were referred to urologists with haematospermia as a primary symptom and noted that MRI was a significant predictor of prostate cancer (PCa) diagnosis after adjusting for age, PSA and DRE results (OR 14.15, $p = 0.001$).

Haematospermia as a presenting symptom of malignancy is not a new concept. Han et al. reported in a large ($n = 26,126$) PSA screened population that haematospermia was a significant predictor of prostate cancer diagnosis irrespective of age, PSA and DRE results (OR 1.73, $p = 0.054$) [2]. Due to lack of a control group, we could not perform similar investigations on our population of patients, therefore, it is difficult to draw any conclusion regarding the association of haematospermia with PCa. We have observed that 12 men (9.6%) had PCa in our group. Three of these patients were diagnosed with significant Gleason ≥ 8 prostatic adenocarcinoma despite low PSA and/or normal digital rectal examination. These patients, however, had abnormal MRI results suspicious for PCa, which strongly influenced the clinical decision of subjecting these men to TRUS prostate biopsies. A literature review performed by Ahmad et al. revealed a total of 33 tumors in 931 investigated haematospermia patients [6]. These tumors were prostatic of origin ($n = 25$), seminal vesicle ($n = 6$), testicular ($n = 1$) and epididymal ($n = 1$). We have compared the detection rate of PCa in our group versus the detection rate of PCa in a similar group but without haematospermia as described by Han et al. The characteristics of both groups are presented in Table 2. The small sample size ($n = 12$) of PCa patients with haematospermia in our study makes statistical analysis impossible, however, when compared with Han et al.'s cancer control group without haematospermia it appears that the detection rate of PCa is higher in our haematospermia group (6.5% vs. 9.6%). This is in concordance with the results of the Han et al. study, dem-

onstrating that the detection rate of PCa was higher (13.7%) in their haematospermia group vs. 6.5% in the screened group without haematospermia. The presence of haematospermia in their analysis closely approached statistical significance in the multivariate logistic regression model after adjusting for age, PSA and DRE (OR 1.73, $p = 0.54$). The study concluded that haematospermia is a rare phenomenon in a cancer screening population. Its presence warrants thorough cancer investigations as probably it is associated with a PCa. In our study, we have looked at men with recurrent haematospermia and failed to observe its significance in PCa diagnosis. In the univariate and multivariate logistic regression model, persistent haematospermia defined as 4 or more episodes or lasting longer than 6 months, was not an independent predictor of cancer diagnosis (OR 0.20, $p = 0.15$).

Different statistical results between our study and the Han et al. study might be due to a few factors. We have had a relatively small group sample, which possibly leads to an underpowered (type 2 error) study. Furthermore, significant demographical heterogeneity (presence of young <40 years old men in our group) makes comparison difficult. Finally, the screened population is biased to have higher PCa detection rate and therefore is not an ideal control group. In the largest series of haematospermia, Leary and Aguilo reported in 1974, that only 6 (4%) of 200 studied men had PCa diagnosed 8 to 12 years after initial evaluation. Most of them, aged 20 to 74 had an unremarkable genitourinary evaluation and history. During the long follow-up period (5 to 23 years) nearly one third of them experienced recurrent haematospermia [17].

Over the years, MRI has revolutionized the ability to determine the etiology of haematospermia. MRI, apart from detecting neoplasms, is capable of identifying changes in anatomical structure secondary to endocrine therapy, radiation, inflammatory disorders and hemorrhage. In 15 patients, studied by Maeda et al. with MRI, benign abnormalities were detected. The majority of these changes were seminal vesicle dilatation most likely due to inflammatory/infective change and multiple cysts of the seminal vesicles. In our study, 27 patients were identified with benign conditions, which could explain haematospermia. Nine patients (8.4%) were diagnosed with seminal vesicle cysts. This represents a significantly smaller number than reported in the literature. Li et al. described volume changes of seminal vesicles in 31.4% of 102 studied patients with persistent haematospermia [18]. Contrary to ultrasound, MRI has the unique ability to differentiate between old and new hemorrhages in the distal area of the seminal

tract. In our cohort of patients, we have observed one diagnosis of fresh intra-prostatic hemorrhage and one 'old' clot around the seminal vesicles.

The main strength of our study is the number of cases accrued which amounts to the largest series published of MRI investigated haemospermia patients. The main limitation of this series is a reliance on correct documentation in retrospective data collection. However, this is an inherent difficulty in all retrospective studies and multiple checks were made to ensure maximum accuracy.

Prostate cancer is uncommon in patients who pres-

ent with haemospermia. MRI seems to be excellent adjunct to investigate patients presenting with this condition as patients with a normal PSA and DRE may still harbour clinically significant prostate cancer. Duration of haemospermia does not predict the presence of prostate cancer. The results have highlighted the need to address haemospermia investigation protocols and have guided our service development.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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