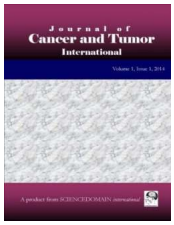


Journal of Cancer and Tumor International
3(1): 1-21, 2016, Article no.JCTI. 21431
ISSN: 2454-7360

SCIENCEDOMAIN *international*
www.sciencedomain.org

A Review on Primary Angiosarcoma of the Prostate Gland: An Update

Anthony Kodzo-Grey Venyo[1*]

[1]Department of Urology, North Manchester General Hospital, Delaunay's Road, Manchester, United Kingdom.

Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JCTI/2016/21431
Editor(s):
(1) Nicole Riddle, Department of Pathology, The University of Texas Health Science Center (UTHSCSA), USA.
Reviewers:
(1) Anthony Cemaluk C. Egbuonu, Michael Okpara University of Agriculture, Umudike, Nigeria.
(2) Pasquale Cianci, University of Foggia, Italy.
(3) Rodrigo Crespo Mosca, Sao Paulo University, Brazil.
(4) Sultan Ayesh Mohammed Saghir, University Saina Malaysia, Malaysia.
Complete Peer review History: http://sciencedomain.org/review-history/12629

Review Article

Received 16th August 2015
Accepted 23rd November 2015
Published 10th December 2015

ABSTRACT

Primary angiosarcoma of the prostate (PASOP) is a very rare tumour which most clinicians have not encountered and may be unaware of Literature of PASOP was reviewed by obtaining information from various internet data bases including: Google, Google Scholar, Educus, and PUB Med. Less than 20 cases of PASOP have been reported. PASOP may present in a male child or adult with lower urinary tract symptoms, dysuria, haematuria, pain and constipation. There may be in some cases a history of prior radiotherapy for adenocarcinoma of prostate. Diagnosis is based upon histological examination of prostate biopsy specimens which tend to reveal: proliferative vascular channels that are lined by atypical multi-layered or atypical solid endothelial cells, variable pleomorphic tumour cells ranging from spindle cells to large/plump cells; nuclei which are large and pleomorphic and which contain clumped chromatin and prominent nucleoli; mitotic figures of which some may look atypical are frequently seen. PASOPs on immunohistochemical staining tend to stain positively for CD34, Factor 8 (Factor VIII), Vimentin. PASOPs on immunohistochemical staining tend to exhibit negative staining for PSA, Keratin and S-100. Surgical resection with surgical margins that are clear of tumor has been shown to be the treatment associated with a chance of long-term survival but a number of reported cases of PASOP at the time of initial diagnosis had presented with metastatic disease or locally advanced disease and curative surgery

**Corresponding author: Email: akodzogrey@yahoo.co.uk;*

with clear surgical margins has been impossible. Various adjuvant therapies had been reported but on the whole the prognosis has been poor. There is on the whole no consensus opinion on the best management options for all stages of the disease. PASOP is a rare aggressive disease. Clinicians should report cases of PASOP they encounter and should enter them into a multi-centre trial to find the best treatment option. Perhaps if patients who develop relapse disease who had previously undergone radiotherapy for prostate cancer undergo further biopsies of prostate may be new cases of PASOP would be diagnosed in the new biopsy specimens.

Keywords: Primary angiosarcoma; prostate gland; CD 34; factor VIII-related antigen; vimentin; spindle cells.

1. INTRODUCTION

Primary angiosarcoma of the prostate gland (PASOP) is an extremely rare malignancy which can afflict children as well as adults. In view of the rarity of PASOP most clinicians would be unaware of the presentation, the diagnostic features as well as the biological behaviour of the disease. The question needs to be asked whether or not a number of patients globally do develop angiosarcoma of the prostate but these are not diagnosed because on the whole most patients who had undergone external beam radiotherapy or brachytherapy for adenonocarcinoma of the prostate gland with curative intent upon relapse of their symptoms do not routinely undergo repeat prostate biopsies because they are all presumed to have developed relapse of their adenocarcinomas. Dedifferentiation of toti-potential cells in the prostate gland could possibly occur following radiotherapy to the prostate gland and the prostate gland could subsequently develop different types of sarcoma which may occur together with adenocarcinoma of the prostate gland or perhaps the radiotherapy treatment could possibly have effectively cured the adenocarcinoma but a de novo sarcoma of the prostate gland alone may ensue curative treatment of adenocarcinoma of the prostate following radiotherapy of the prostate. Even though a number of cases of PASOP have been reported which had not been associated with previous radiotherapy, a handful of cases of PASOP have been reported associated with previous radiotherapy to the prostate gland for adenocarcinoma. The ensuing literature review of PASOP is divided into two parts: (A) Overview and (B) Miscellaneous narrations and discussions from some reported cases of PASOP

2. METHODS

Various internet data bases were searched including: Google, Google Scholar, Educus, and PUB Med. The search words used included: Primary angiosarcoma of the prostate gland, Angiosarcoma of prostate, prostatic angiosarcoma. Forty-eight references were identified with information relevant to primary angiosarcoma of the prostate gland which was used for the literature review (last information was accessed at the end of July 2015).

3. RESULTS

3.1 Overview

3.1.1 General

Primary angiosarcoma of the prostate gland is a very uncommon tumour with less than 20 cases so far reported in the literature [1].

3.1.2 Definition

3.1.2.1 Aetiology/pathogenesis

The exact cause of all the cases of primary angiosarcoma of the prostate cannot be confirmed for certain. It may be conjectural; however, it could be said that some of the cases of PASOPs may be de novo carcinomas but others could have resulted from mutation of TP53 tumour suppressor gene following radiotherapy to the prostate gland for adenocarcinoma of the prostate gland or radiotherapy as treatment for any other malignancy close to the prostate of which the prostate gland had been in the radiation field. What is known is that some of the reported cases of PASOP have been associated with previous radiotherapy treatment for adenocarcinoma of the prostate gland [2] The criteria to establish a diagnosis of radiotherapy-induced (radiation-induced) sarcoma, has been stratified by Cahan et al. [2] as follows [1]:

- The tumour must arise in the area which had been radiated previously.

- There must be a latent period in years following the radiotherapy preceding the development of the tumour.
- The diagnosis of sarcoma must be confirmed by means of histological examination.

Furthermore, in 2012 it had been stated [3] that the association of PASOP with radiotherapy (radiation therapy), may be weak. With this in mind if there is no direct link of a PASOP with radiotherapy then such a case of PASOP not linked with radiotherapy could be regarded as a de novo sarcoma unless there is evidence of any other direct association with the case of PASOP.

Chen et al. [4] in 1979 stated that the direct oncogenic effects of ionizing radiation and the prolonged stimulation of the cell during the process of tissue repair of damaged tissue which results from radiation induced ischaemic change have been postulated to play a role in the development of angiosarcoma. Khaliq et al. [3] had intimated that other different factors had been linked with the development of angiosarcoma and these include chronic lymph oedema and exposure to chemicals like arsenic, thorium dioxide and vinyl chloride; however, from their review of the literature none of the reported cases of PASOP had had an exposure to chemicals.

Cahan et al. [2] had iterated that radiation induced sarcoma could occur in an area which had been previously radiated within a latent period which is as long as 7 years. Association of angiosarcoma and radiotherapy had previously been reported. In one case Nanus et al. [5] and in the other case, Navon et al. [6] reported a case of angiosarcoma of the urinary bladder following therapeutic radiotherapy for adenocarcinoma of the prostate gland.

With regard to angiosarcoma of the prostate gland, Khaliq et al. [3] pointed out that their review of the literature had revealed that out of the ten cases of primary angiosarcoma of the prostate that had been published in the literature by the time of their publication only 3 of the patients had previously undergone radiotherapy when the serum PSA levels were within normal range or PSA was not detectable [7-9] and based upon this they were of the opinion that the association between radiotherapy and the development of angiosarcoma of the prostate was weak.

Other reports of an association between radiotherapy and an increased risk for the development of soft tissue sarcoma following radiotherapy have been reported in association with: breast cancer [10-12].

Moon et al. [13] reported an increased risk for the development of a second primary cancer of the urinary bladder, rectum, gastrointestinal tract, brain, lung, lymphoma as well as leukaemia in patients who had been diagnosed as having carcinoma of the prostate gland 5 years pursuant to radiotherapy in comparison to those who did not undergo radiotherapy in a study. Moon et al. [13] also reported that the same study had shown that men who had undergone radiotherapy in the form of isotope or radioactive implants did not have an increased risk for the development of a second primary cancer. Khaliq et al. [3] observed that in the large cohort study undertaken by Moon et al. [13] no enhanced risk for the development of angiosarcoma of the prostate was reported.

Bagchi Sanjeet [14] reported in 2014, that new research had shown that two novel genes, PTPRB and PLCG1, are associated with the development of angiosarcoma.

3.1.2.2 Epidemiology

Age:

- PASOP may affect children and adults

General comments on the epidemiology:

Khaliq et al. [3] had stated that: PASOP is very rare and the progression as well as its prognosis on the whole is not clearly understood; A peak incidence of PASOP had been observed to be between 40 years and 50 years with a mean age of 40 years in the literature; one case of PASOP had afflicted a 2 years and 9 months old child; Smith et al. [15] had reported two cases of PASOP and at that time they did find two other cases in the literature from 1889 to 1986 [16] [17]; Chan et al. [18] reported a 35-year-old Chinese man who had PASOP which was said to be the 5th case of PASOP to be reported; Oliva Encina et al. [19] reported a 31-year-old man with PASOP which was considered to be the 6th case of PASOP; Chandran and Wolsh [7] reported a man who was diagnosed as having PASOP, who had ten years earlier undergone radiotherapy as treatment for adenocarcinoma of the prostate gland and this was reported as the

7th reported case of PASOP; Lee et al. [20] reported a 19 year-old man who was diagnosed as having teratoma of the prostate gland which was resistant to chemotherapy and who was subsequently diagnosed as having developed angiosarcoma of the prostate gland, as the 8th reported case of PASOP; Guo et al. [8] reported the 9th case of PASOP in a patient who had undergone radiotherapy 4 years earlier; Khaliq et al. [9] reported a 73-year-old man who had undergone brachytherapy for adenocarcinoma of the prostate gland 8 years preceding his subsequent diagnosis of having angiosarcoma of the prostate gland together with adenocarcinoma of the prostate and the case was reported as the 10th case of PASOP;

The aforementioned few anecdotal case reports would be considered not enough for a full understanding of the epidemiology of PASOP. In view of this there is the need for clinicians to report new cases of PASOP that are diagnosed so that the biological behaviour and epidemiology of the disease can be fully understood.

3.1.3 Presentation [7]

Patients with PASOP may present with:

- Lower urinary tract symptoms, urinary frequency, reduced urinary stream.
- Dysuria.
- Pain.
- Haematuria.
- Constipation.

3.1.4 Findings on clinical examination

Clinical findings in PASOP tend to be non-specific and these may include the following:

- A normal benign feeling prostate, a nodule or nodules on the prostate, enlarged prostate which may or may not extend beyond the prostate.
- There may be blood seen at the external urethral meatus in cases of PASOP associated with haematuria.
- If the patient has retention of urine then the urinary bladder would be palpable or the supra-pubic region may be dull on percussion.

3.1.5 Laboratory investigations

Urine analysis, microscopy, culture and sensitivity

- Urinalysis, urine microscopy, urine culture and sensitivity are part of the general assessment of the patient to find out whether or not there is any urinary tract infection which could be treated prior to biopsy or treatment of PASOP.

3.1.6 Haematological investigations

- Full blood count and coagulation screen are non-specific tests that are carried out in the general assessment of the patient but usually there would be no specific abnormality related to the PASOP. Nevertheless, when a patient develops massive bleeding following biopsy of the prostate or trans-urethral resection of the prostate the patient could develop anaemia or even eventual evidence of disseminated intravascular coagulopathy.

3.1.7 Biochemistry investigations

- Serum urea, renal function tests, liver function tests and bone profile are investigations that form part of the general assessment of the patient and these may be normal or abnormal depending upon whether the patient has retention of urine or metastatic disease.
- Serum prostate specific antigen and serum prostate-specific acid phosphatase would tend to be normal but in situations when there is mixed tumour of PASOP associated with adenocarcinoma of the prostate gland then the serum PSA level may be raised.

3.1.8 Radiological investigations

Ultrasound scan

- Ultrasound scan of abdomen and pelvis findings may be variable depending upon the state and stage of the disease and this may show normal upper renal tracts and normal urinary bladder, or unilateral/ bilateral hydronephrosis, trabeculated urinary bladder, a lesion/mass in the prostate which may be localized to one lobe or both lobes or which may extend and invade the bladder or the seminal vesicle or extend beyond the capsule of the prostate towards the rectum or pelvic side wall. Ultrasound scan of the abdomen may show evidence or absence of a metastatic lesion in the liver or enlarged lymph nodes in the pelvis or abdomen.

- Trans-rectal ultra-sound scan of prostate can be done to assess the prostatic lesion and as a guide to taking biopsies of the prostate for histological examination to establish a diagnosis. Trans-rectal ultrasound of prostate would illustrate the echogenicity of the prostate gland including hypo-echoic areas and iso-echoic areas as well as the number of hypo-echoic areas. With the aid of trans-rectal ultrasound scan any abnormal looking areas of the prostate gland identified would be included in the biopsy.

Computed tomography (CT) scan

- CT scan of abdomen, pelvis and thorax tends to be done as part of full assessment of the extent of the tumour. CT scan of thorax, abdomen and pelvis can be done in the initial staging of the disease and also in the follow-up of the patient following treatment to confirm presence or absence of metastatic disease.

Magnetic Resonance Imaging (MRI) Scan

- MRI scan of pelvis, abdomen and thorax is a useful radiological investigation to assess the prostatic lesion and to define the extent of the tumour. MRI scan of thorax, abdomen and pelvis can be used for the initial staging of the tumour as well as in the subsequent follow-up of the patient in assessing for presence or absence of metastatic disease.

Isotope Bone Scan

- Isotope bone scan is a useful investigation to determine whether or not there is metastasis in the bone. If a patient complains of back ache and bony metastasis is suspected, isotope bone scan is one of the investigations that can be done to confirm absence or presence of metastasis in the bone.

3.1.9 Macroscopic features

- Gross examination of the prostate gland in PASOP may reveal a tan-brown prostatic tumour [1,7] with extensive necrosis and perhaps bleeding may be seen from the tumour

Microscopic examination of PASOPs would tend to show the following (see Figs. 1, 2, and 3 for example [1,7]:

- Proliferative vascular channels that are lined by atypical multi-layered or atypical solid endothelial cells.
- Variable pleomorphic tumour cells ranging from spindle cells to large/plump cells.
- Nuclei which are large and pleomorphic and which contain clumped chromatin and prominent nucleoli.
- Mitotic figures of which some may look atypical are frequently seen.

3.1.10 Immunohistochemistry characteristics

Positive Immunohistochemistry

PASOPs on immunohistochemical staining tend to stain positively for the following:

- CD34
- Factor 8 (Factor VIII)
- Vimentin

Negative Immunohistochemistry

PASOPs on immunohistochemical staining tend to exhibit negative staining for the following:

- PSA
- Keratin
- S-100

3.1.11 Differential diagnosis

Other forms of carcinomas of the prostate gland that need to be differentiated from PASOP include: carcinosarcomas, osteosarcomas, chondrosarcomas, leiomyosarcomas, rhabdo-myosarcomas, synovial-cell sarcomas, adenocarcinomas admixed with other types of sarcomas, lymphoepithelioma-like carcinoma.

3.1.12 Treatment

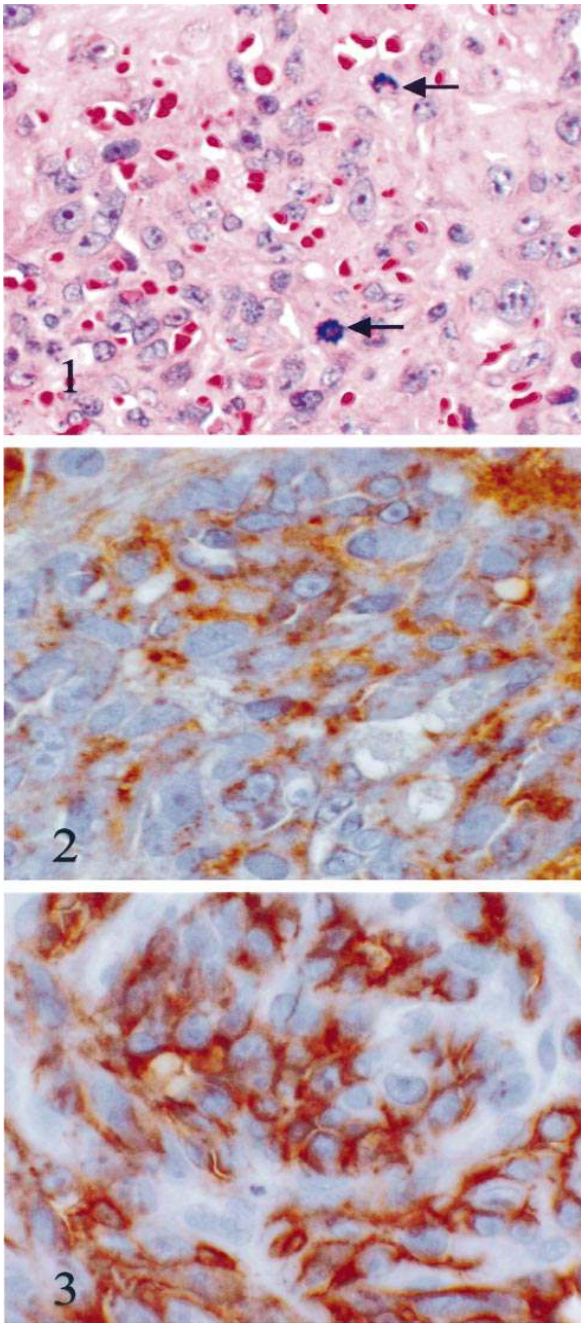
3.1.12.1 General comments on treatment

In view of the fact that very few cases of PASOP have been reported and the fact that globally no clinician has the experience of managing many cases of PASOP, there is no consensus opinion on the management of PASOP. Important facts that need to be taken into consideration include the size of the prostatic tumour, whether the tumour is localized and can be surgically excised completely by means of radical cystoprostatectomy or radical prostatectomy to be able to achieve complete tumour clearance at the surgical margins, whether or not there are

any lymph nodes involved by the tumour or there are metastases. With regard to the first ten cases of PASOP that had been reported, six patients had undergone radical cystoprostatectomy and two patients had undergone sub-total resections of the prostate gland, one patient died shortly after his admission to hospital, and one patient was lost to follow-up. With regard to the six patients reviewed by Khaliq et al. [3] who had undergone radical cystoprostatectomy surgical margin clear of tumour was achieved in only one patient. Three of the patients who had undergone cystoprostatectomy had also received adjuvant chemotherapy which had comprised of doxorubicin in one of the cases, experimental thalidomide in another patient, and ifosfamide and doxorubicin in the third patient. Khaliq et al. [3] noted that none of the patients had been treated by means of radiotherapy presumably because of the notion that radiotherapy to adenocarcinoma may induce angiosarcoma or other types of prostatic tumours. One patient who had undergone trans-urethral resection of prostate [7] and removal of blood clots from the urinary bladder developed severe haematuria post operatively requiring transfusion with several units of blood. He developed disseminated intravascular coagulopathy and died. Histological examination of the resected specimen was reported as showing angiosarcoma of the prostate gland. Lessons learnt from this case is the fact that angiosarcoma is a vascular lesion which can bleed severely in view of this necessary precautions would have to be taken by the clinician to avoid/minimise or promptly treat such bleedings in the form of pre- or post -operative selective angiography and selective/super-selective embolization of the bleeding artery to the prostatic tumour. In the aforementioned case the diagnosis was known perhaps after the patient had died. Even though some people are of the view that the evidence for radiotherapy induced angiosarcoma of the prostate is weak, it would be argued since some cases of angiosarcoma following radiotherapy have been reported one should always consider the possibility of angiosarcoma of the prostate developing many years after undergoing radiotherapy for adenocarcinoma of prostate. If a patient who had undergone radiotherapy for carcinoma of the prostate gland subsequently presents with lower urinary tract symptoms or haematuria, a digital rectal examination should be undertaken irrespective of the level of serum PSA and if a nodule or mass is palpable on the prostate then ultrasound-guided biopsy should be undertaken of the mass. If the histology of the biopsy specimen confirms angiosarcoma of the prostate then it would be recommended that the interventional radiologist should be involved in a multi-disciplinary approach plan of management so that a possible pre-operative or post-operative embolization of the artery supplying the tumour is undertaken to avoid or minimize excessive exsanguinating bleeding.

3.1.12.2 Treatment of localized disease

Considering the fact that very few cases of PASOP have been reported one cannot be absolutely sure what the best treatment option for this aggressive disease should be. Perhaps lessons learnt from the management of angiosarcomas could be used as a guide for the management of angiosarcoma of the prostate gland. It would appear that radical surgery of complete resection with tumour margins that are clear of tumour should be the treatment of choice but this can be hampered by the size of the tumour, invasion of other tissues by the tumour, as well as the relationship of the tumour to nearby critical organs and these factors have tended to be associated with prognosis. [21-23] With regard to a number of patients who had developed recurrent angiosarcoma, Lahat et al. [24] had observed that patients who had undergone surgical excision of the tumour for localized disease with histopathological evidence of complete resection of tumour and absence of tumour at the surgical resection margins had improved survival in comparison with those patients who had tumour at the resection margins. On the whole it is usually the aim of every surgeon to achieve complete resection of tumour in any type of malignancy as a treatment of curative intent if the tumour is resectable. Khaliq et al. [3] had stated that on the whole adjuvant radiotherapy had been recommended for the treatment of sarcomas with the aim of reducing or preventing local recurrence in cases of sarcoma but they pointed out that randomized controlled trials had not been undertaken related to the use of adjuvant radiotherapy in sarcomas. However, Khaliq et al. [3] pointed out that Pawlik et al. [23] had reported an overall survival in patients who had had adjuvant radiotherapy. Controversies exist regarding the place of the use of adjuvant chemotherapy in the treatment of sarcomas with some reports documenting improved survival [25-27] and others not finding any improved survival with adjuvant chemotherapy [28].



Figs. 1, 2, and 3. Fig. 1. The tumor consisted of pleomorphic cells and large nuclei with clumped chromatin and prominent nucleoli, Mitoses are easily seen (arrows). Vascular channels lined by atypical endothelial cells are present within the tumor (hematoxylin-eosin, original magnification, X 400). Figs. 2 and 3. Tumor cells show positive staining for factor VIII-related antigen (Fig. 2) and CD 34 (Fig. 3) (immunohistochemistry original magnification, X 400)

Figures 1, 2, and 3 have been reprinted from: Chandan V S, Wolsh L. Postirradiation Angiosarcoma of the Prostate Arch Pathol Lab Med 2003 Jul; 127(7): 876 – 878 with permission from Archives of Pathology & Laboratory Medicine Copyright 2003 College of American Pathologists. This permission is exclusive to this request. Additional usage of any printed or electronic material for which the Archives of Pathology & Laboratory Medicine owns copyright would require permission from the editorial office

3.1.12.3 Treatment of metastatic disease

In view of the very few cases of PASOP that have been reported there is no consensus opinion on the best treatment option or useful options of its treatment. It would appear as if there is no consensus opinion in the choice of management regimes for treating angiosarcomas afflicting other organs too. Khaliq et al. [9] stated that on the whole cytotoxic chemotherapy with the use of anthracyclines, ifosfamide, and taxanes have been the primary treatment of choice for metastatic angiosarcomas on the whole. Mocellin et al. [29] had stated that generally the use of combination chemotherapy in the treatment of metastatic angiosarcoma had been associated with increased incidence of toxicities and its use had failed to provide improvement in the overall survival of patients with angiosarcoma. Generally the use of various combination chemotherapeutic regimens had been associated with various response rates [30-32]. Some of the other therapeutic agents, that had been used include: VEGFA, monoclonal antibody, bevacizumab [33], interferon-α, [34], [35] interferon-α in combination with doxorubicin. [36] Interleukin-2 has been used as a single agent as well as in combination with chemotherapy or with radiotherapy, [37]. Khaliq et al. [9] had stated that at the moment, interleukin-2 and interferon-α, are only being used in clinical trials and on the whole their use outside clinical trials has not been routinely undertaken. The aforementioned information would strongly confirm that there is a great need for all cases of angiosarcoma of the prostate gland to be reported and entered into a global multi-centre trial in order to find the best treatment option for the disease and to ascertain their biological behaviour.

3.1.13 Outcome

In view of the fact that very few cases of PASOP have so far been reported in the literature it would be argued that the true biological behaviour of PASOP would not be known. Nevertheless, what is known is that six patients (60%) out of the first ten reported patients, who were diagnosed as having PASOP had died within 9 months of the diagnosis of their tumours and three of the patients were free of their disease (without residual local disease or metastasis) over a period of 16 months, 24 months and 36 months respectively but one of the patients was lost to follow-up. The aforementioned outcome would indicate that perhaps mortality in cases of PASOP should be expected to be high unless a treatment option is found that would improve the prognosis. Whether or not the biological behaviour of PASOP would be similar to the prognosis associated with treatment of angiosarcomas of other sites of the body would not be known at present. However, it has been reported that the five-year survival for soft-tissue sarcomas has ranged between 50% and 60% [29] and that the five-year survival for angiosarcomas at any site was 35%. [21] [22] [38] Young et al. [28] had stated that suspected factors for poor prognostication for other types of soft-tissue sarcomas include: tumour size greater than 5 cm, the histological grade of the tumour, advanced age, location of angiosarcomas in retroperitoneal locations, presence of metastases, and poor patient performance.

3.2 Miscellaneous Narrations and Discussions from Some Reported Cases (see table 1 for reported cases)

Chandan and Wolsh [7] reported a 77-year-old man who had presented in 2002 with visible haematuria, urinary frequency, dysuria, and bladder spasms. He was asymptomatic otherwise. Ten years earlier in 1992 he had undergone external beam radiotherapy for stage B, Gleason 7 adenocarcinoma of the prostate gland and since then he had been having follow-ups for his previously treated adenocarcinoma of the prostate gland. His latest serum PSA in 2002 was 0.0023 ng / ml (normal range 0-0.04 ng / ml). His clinical examination on the whole was normal. He had a CT scan of abdomen, pelvis, and thorax which did show a large mass arising from the prostate gland. There was no evidence of metastasis in his chest X-ray and CT scan of the thorax. He underwent urethrocystoscopy which revealed a tri-lobar prostatic enlargement with irregular prostatic enlargement encroaching upon the prostatic urethra. There was also blood clot in his urinary bladder. He underwent trans-urethral resection which removed the protruding prostatic tissue in his prostatic urethra and prostatic tissue in the base of the urinary bladder. The specimen was sent for histological examination. He continued to have visible haematuria post-operatively and was given several units of blood transfusion. He developed disseminated intravascular coagulopathy and died 4 days after his surgical operation. Gross examination of the specimen of the resected prostate, did reveal a 15 grams tan-brown soft tissue, which had been mixed with blood clot. Histological examination showed that less than

10% of the specimen was viable tissue and the remaining approximately more than 90 percent of the tissue, was necrotic. The viable tissue was found to comprise of vascular channels that had been lined by atypical endothelial cells which had been encompassed by spindle-shaped cells. The tumour cells were adjudged to be pleomorphic and they had varied from elongated and spindle-shaped cells to large and plump cells. The nuclei were observed to be large and pleomorphic and they had clumped chromatin and the nucleoli were prominent. Mitotic figures were frequently observed and some of the mitotic figures looked atypical (see Fig. 1). The histological examination also revealed that the area of the prostatic urethra did show prominent von Brunn nests without showing any evidence of atypia. Immunohistochemical staining of the specimen had revealed positive staining for factor VIII-related antigen (see Fig. 2), CD 34 (see fig. 3), and vimentin in the tumour cells. Based upon the aforementioned findings a diagnosis of angiosarcoma of the prostate gland was made. Chandan and Wolsh [7] stated the following:

- In order to establish a diagnosis of radiotherapy-induced angiosarcoma, Cahan et al. [2] had suggested the ensuing criteria: (a) the sarcoma should arise in an area which had been previously subjected to radiotherapy treatment; (b) a latent period in years must exist between the time of radiotherapy treatment and the development of the sarcoma; (c) the sarcoma must be diagnosed by means of histological examination. Based upon the Cahan et al. [2] criteria their patient had satisfied the criteria for the diagnosis of radiotherapy-induced angiosarcoma of the prostate gland.
- Kim et al. [12] had reviewed 66 reported cases of angiosarcoma and reported that the commonest primary cancer for which the radiotherapy treatment was given was carcinoma of the breast which constituted 44% of the cases; and gynaecological cancer constituted 21% of the cases for which radiotherapy was given. Eighty-five percent of the radiotherapy-induced angiosarcoma had developed in cutaneous areas; the median age at diagnosis of the angiosarcoma was 65 years; the median latent period from the time of the previous radiotherapy and development of angiosarcoma was 96 months; the median survival period from the time of the diagnosis of the angiosarcoma was 12 months.
- The causal relationship between radiotherapy and the development of angiosarcoma had been discussed previously; nevertheless, Cafiero et al. [39] had indicated that there is little doubt that bona fide post-radiotherapy-induced angiosarcoma does occur. Chen et al. [4] had intimated that apart from the direct oncogenic effect of direct irradiation, prolonged cellular stimulation during repair of tissue damage that has emanated from radiotherapy induced ischaemic change may have a role to play in the development of angiosarcoma.
- Their observations from the 6 previously reported cases of post-irradiation-induced angiosarcoma of the prostate gland were as follows: At the time of diagnosis of angiosarcoma of the prostate, the patients' ages had ranged between 2 years and 65 years and the mean age was 34.5 years; one case had involved a child who was aged 2 years and 9 months; the presenting symptoms of the patients had included dysuria and haematuria; with regard to outcome, 3 patients had died of the angiosarcoma within the first 6 months of the initial diagnosis, 2 patients were free of angiosarcoma for a period of 24 months and 36 months, and one patient did not have a follow-up.
- Navon et al. [6] had reported 1 case of post-radiotherapy-induced angiosarcoma of the urinary bladder which had developed 13 years after the patient had undergone radiotherapy for adenocarcinoma of the prostate gland; they would speculate that as radiotherapy for prostate cancer improves survival, the incidence of post-radiotherapy angiosarcoma of the prostate gland should be expected to increase; Mart et al. [38] had estimated the risk for the development of post-radiotherapy-induced sarcoma after a long period of follow-up to be from 0.03% to 0.8%; literature review which had compared the mortality risks of chemotherapy, general surgery and anaesthesia had indicated that the risk of post radiotherapy sarcoma was not worse and that concerns related to the possibility of the development of post-radiotherapy sarcoma should not be an influential factor in taking management decisions; pathologists would need to be aware of

the possibility of post-radiotherapy angiosarcoma in patients who present with haematuria and / or dysuria when they had previously undergone radiotherapy.

Khaliq et al. [9] in 2012 reported a case of angiosarcoma of the prostate which was associated with adenocarcinoma of the prostate and they stated that from their search of the literature, their case was the 10th case of angiosarcoma to be reported in the literature because their literature search had revealed 9 previously reported cases [9].

Smith et al. [15] in 1986 reported 2 cases of angiosarcoma of the prostate gland in patients who were aged 42 years and 60 years. Immunohistochemical staining of the tumors for factor VIII associated antigen was positive in the two cases and this in the opinion of the authors was very useful with regard to the confirmation of the diagnosis in one case which was otherwise a poorly differentiated tumor. One of the patients who underwent surgical excision was alive without any evidence of recurrent tumor 2 years after he had undergone surgical excision of his tumor. On the other hand, the other patient who had presented with unresectable tumor died 6 months after he had presented. Smith et al. [15] stated that even though angiosarcoma constitutes less than 2 percent of sarcomas of the prostate gland it should be considered in the differential diagnosis of poorly differentiated sarcomas, especially those that occur in adults [15].

Campschroer et al. [40] reported a 69-year-old man who presented with voiding symptoms which had culminated in retention of urine. Eight years prior to his admission, he had been diagnosed with a Gleason 6 adenocarcinoma of prostate and his initial serum prostate-specific antigen (PSA) level was 6.6 ng/ml. He underwent brachytherapy and his most recent serum PSA about 8 years pursuant to his brachytherapy was 0.11 ng/ml. He underwent cystoscopy and trans-urethral resection of prostate on two occasions as well as trans-rectal ultrasound guided biopsies of the prostate of a cystic mass arising from the prostate. Histological examination showed necrosis and extensive inflammation in the first resected prostatic tissue and lymphoid tissue and necrosis in the biopsy specimen. Histological examination of the second resected prostatic specimen revealed features consistent with angiosarcoma of the prostate with evidence of inflammation and necrosis. Immuno-histochemical staining of the tumor showed positive staining for CD31, CD34, vimentin, and factor VIII but negative staining for PSA. His pubic bone was involved by the tumor. He was adjudged to be unfit to undergo surgery or chemotherapy. He died within 4 months of his diagnosis.

Campschroer et al. [40] searched for literature on angiosarcoma of the prostate gland using various internet data bases. They included their case of PASOP in the review. Campschroer et al. [40] identified 13 cases of angiosarcoma of the prostate gland and of the 13 cases they had included in their analysis, they had found that the earliest six publications had lacked essential data in their opinion. They stated the following:

- Out of the 13 patients, four patients did have a history of having undergone radiotherapy treatment previously.
- With regard to five of the patients their treatment had consisted of radical surgery with or without chemotherapy. With regard to eight of the cases curative treatment was either not reported or not possible.
- The mean follow-up was only for a period of one year.

With regard to outcome, four of the 13 patients had died within one year of their diagnosis, irrespective of the choice of treatment. One patient, who had undergone a combination of radical surgery and adjuvant chemotherapy, was still alive 36 months pursuant to his treatment.

Campschroer et al. [40] concluded that their patient was the first case of angiosarcoma of the prostate gland following primary brachytherapy to be reported; angiosarcoma may develop more often in the future due to the widespread use of brachytherapy and radiotherapy of the prostate gland; the current guidelines on the treatment of angiosarcoma recommend radical surgery in the case of local disease as the primary treatment of choice.

Table 1. A list of reported cases of primary angiosarcoma of the prostate gland

Authors/ reference/ year	Age/ presentation	Metastasis /no metastasis	Exposure to cancer radiotherapy or not	Histopathology of tumour	Treatment	Outcome
Smith et al. [15] 1986	60 years; reduced stream of urine, urinary frequency	Local lymph node tumour involvement	No	Sheets of solid or round pleomorphic cells which had abundant cytoplasm; enlarged hyperchromatic pleomorphic nuclei; the tumour cells were lining slit-like spaces which contained blood with prominent tufts; Immunohistochemistry was positive for factor VIII.	Radical cystoprostatectomy & partial resection of pubic bone, uretero-ileal diversion plus pelvic lymph adenectomy. The tumour had extended to the pelvic wall margin & was not resectable; 12 out of 22 lymph nodes contained tumour deposits, Adjuvant chemotherapy could not be given because of the patient's poor functional status	He died at 6 months
Smith et al. [15] 1986	42 years; Pain	No metastasis	No	Pleomorphic elongated spindled cells; the nuclei of the tumour had varied from small and pyknotic to large and vacuolated and with clumped chromatin which contained one or more nucleoli; there were rare vascular structures which had been lined with maglibnant cells; immunohistochemical staining of the tumour showed positive staining for Factor VIII. The histopathology was adjudged to be consistent with poorly differentiated sarcoma with angiosarcoma with features of angiosarcoma.	He underwent radical cystoprostatectomy wiith lymphadenectomy ureteroileal urinary diversion. The resection of the tumour was complete with the surgical resection margins clear of tumour. He also received adjuvant chemotherapy 2 months after his operation with doxorubicin 70 mg/m2 which was followed by 3-week interval with 75 mg /m2 for a total of 6 courses	Alive & free of disease at 24 months follow-up
Botesco et al. [16] 1902	2 years 9 months; Dysuria & constipation	No metastasis	No	Many neoplastic blood vessels, degenerative connective tissue, lymphocytic infiltrates	Died 1 day after admission	Died 1 day after admission
Salleras and Vilar [17] 1924	32 years; dysuria, constipation & haematuria	No metastasis	No	Many vascular spaces associated with round or spindled, at times multinucleated cells	Was lost to follow-up but was terminally ill	Was lost to follow-up
Chan et al. [18] 1990	35 years; pain, haematuria, urinary frequency	Metastases in lung, spleen, liver & mesentery	No	Nodules of cellular & vascular tumour tissue in the prostate gland; the vascular areas were lined with neoplastic cells which were spindled shaped	He developed massive haematuria after prostate biopsy which required CT guided selective	He died after 5 weeks

Authors/ reference/ year	Age/ presentation	Metastasis /no metastasis	Exposure to cancer radiotherapy or not	Histopathology of tumour	Treatment	Outcome
				and which had frequent mitotic figures; the tumours exhibited positive immunohistochemical staining for factor VIII and vimentin.	angiography and embolization. He died as a sequel of disseminated intravascular coagulopathy (DIC) 4 days later	
Oliva Enchina [19] 2001	31 years; LUTS, urinary urgency, dysuria, incomplete emptying of bladder and dcreased libido	No metastasis	Epithelial angiosarcoma which had infiltrated the urinary bladder and prostate gland. The tumour on immunohistochemical staining stained positively for factor VIII and CD21	Radical prostatectomy with partial resection of the bladder neck and ileo-obturator lymphadenectomy; the margins were not clean (not free of tumour). He received six cycles of adjuvant chemotherapy with ifosfamide and adriamycin as well as radiotherapy	He was alive and free of disease at 36 months follow-up.	Details not available to author.
Chandan and Wolsh [7] 2003	77 years; visible haematuria, urinary frequency, dysuria, and spasm	No metastasis	History of adenocarcinoma of prostate, Gleason 7 which was treated by means of external beam radiotherapy 10 years preceding his presentation. His presenting serum PSA at the time of diagnosis of PASOP was 0.0023 ng/ml (within normal range)	proliferating vascular channels which were lined by atypical endothelial cells that were surrounded by spindle-shaped cells. The tumour cells were noted to be pleomorphic with clumped chromatin and prominent nucleoli. Immunohistochemistry of the tumour was positive for factor VIII, CD34 and vimentin.	Trans-urethral resection of prostate (TURP) and post-operatively developed massive bleeding/haematuria and died 4 days later.	He died at 4 days
Lee et al. [20] 2006	19 years; dysuria, haematuria, & abdominal pain	No metastasis	He had a history of immature teratoma; his serum α-fetoprotein was 192 ng/ml (normal range < 20 ng / ml); his serum ß-Human chorionic	Variably sized glands which were lined either by mature or immature intestinal, respiratory, and neurone epithelial, immature chondroid tissue, mature adipose tissue, and atypically non-proliferating endothelial cells which had sporadic large, hyperchromatic nuclei, and frequent mitotic figures typical of intermediate grade angiosarcoma. The tumour on	At the beginning he was treated for immature teratoma by means of bleomycin, etoposide, and cisplatin chemotherapy; nevertheless, the tumour mass continued to grow; he then underwent radical cystoprostatectomy and formation	He was alive and free of disease at 16 months follow-up

Authors/ reference/ year	Age/ presentation	Metastasis /no metastasis	Exposure to cancer radiotherapy or not	Histopathology of tumour	Treatment	Outcome
			gonadotrophin was 11.6 mIU / ml (normal range < 5 mIU / ml).	immunohistochemistry stained positive for CD31 and CD34.	of an ileal conduit.	
Guo et al. [8] 2009	65 years; haematuria & intractable perineal pain.	No metastasis	He had a history of Gleason 3+3 = 6 adenocarcinoma of the prostate gland which was treated by means of androgen ablation and radiotherapy 4 years preceding his presentation. His serum PSA test at presentation with PASOP showed undetectable PSA	A vasoformative growth which had complex anastomosing channels was seen on histological examination, the tumour cells had highly atypical nuclei that had robust mitotic activity. The tumour exhibited positive immunohistochemical staining for CD31 and CD34	Total pelvic exenteration in which the surgical resection margin was found to be positive for tumour.	He died at 8 months.
Khaliq et al. [9] 2012	73 years; haematuria, diurnal urinary frequency and nocturia.	No metastasis	He had a history of adenocarcinoma of prostate Gleason 3 + 3 = 6 which had been treated by means of external beam radiotherapy and brachytherapy boost 8 years preceding the diagnosis of his PASOP. His serum PSA at the time of the diagnosis of PASOP was 1.2 ng / ml (within normal range).	Proliferating vascular channels were seen on histological examination and these channels were lined by atypical and malignant- appearing endothelial cells, which were adjudged to be consistent with high grade angiosarcoma. The tumour cells on immunohistochemistry exhibited positive staining for factor VIII and CD31. The tissue had been extensively infiltrated by atypical cells that had active mitotic activity.	He underwent total pelvic exenteration and it was noted that the urinary bladder, and seminal vesicles were directly involved by the tumour extension. During the cystoprostatectomy the tumour was observed to be present the urethral margin and the left anterolateral pelvic sidewall. The surgical margins were positive for angiosarcoma and six of thenine pelvic lymph nodes were positive for metastatic adenocarcinoma of the prostate gland with extra-nodal extension	He died at 9 months
Humphrey et al. [41] 2012	67 years; urinary tract obstructive	Presence or absence of	He had radiotherapy for carcinoma of the	Histological examination showed a neoplastic spindle proliferation which formed irregular	TURP for lower urinary tract symptoms	Long term outcome

Authors/ reference/ year	Age/ presentation	Metastasis /no metastasis	Exposure to cancer radiotherapy or not	Histopathology of tumour	Treatment	Outcome
	symptoms	metastasis not mentioned in paper and it would be presumed there was no metastasis.	prostate gland 7 years preceeding the diagnosis of his PASOP	vascular channels which ad dissected through the stroma of the prostate and urinary bladder. Other areas of the tumour were more solid and admixed with the vascular spaces. The vascular channels were lined by neoplastic endothelial cells which had displayed nuclear atypia. The tumour cells on immunohistochemical staining stained positvely for CD31, CD34, and Factor VIII-related antigen. The was no evidence of any residual adenocarcinoma of prostate and immnunohistochemistry had shown negative staining for pan-cytokeratin, prostate specific antigen, and prostate specific acid phosphatase which together confirmed the diagnosis of PASOP and absence of adenocarcinoma of prostate.		not reporter; case was reporter not long after the TURP
Campschroer et al. [40] 2014			Angiosarcoma of prostate in patient who previously had brachytherapy for adenocarcinoma of prostate	Details not available to author.	Details not available to author.	Details not available to author.
Gupta et al. [43] 2014	71 years; lower urinary tract symptoms and visible haemturia.		The patient had radiotherapy to the prostate as treatment for an incidentally diagnosed Gleason 3 + 3 = 6 adenocarcinoma of the prostate based upon routine serum PSA of 4 ng/ml investigation 5 years prior to the diagnosis of PASOP	Details not available to author.	Details not available to author.	Details not available to author.

Authors/ reference/ year	Age/ presentation	Metastasis /no metastasis	Exposure to cancer radiotherapy or not	Histopathology of tumour	Treatment	Outcome
Scharpira et al. [44] 1963	Details not available	Details not available	Details not available	Details not available	Details not available	Details not available
Wick et al. [45] 1989	69 years; details not available	Details not available	Details not available	It was a carcinocarcinoma with other types of sarcoma	Details not available	
Russo et al. [46] 1992	Details not available	Details not available	Details not available	Details not available	Details not available	Details not available
Loque Barona et al. [47] 2000	Case 1 71 years presentation not available to author	Details of metastasis or no metastasis not available but tumour mixed adenocarcinoma; chondrosarcoma, rhabdomyosarcoma, angiosarcoma	Details not available to author	tumour mixed adenocarcinoma; chondrosarcoma, rhabdomyosarcoma, angiosarcoma	Surgery but details of surgery not available	Died at 3 months
Boucher et al. [48] 2000	79 years, details of presentation not available to author	Cervical lymph node metastasis	Details not available to author	Low-grade epithelioid angiosarcoma of prostate ; PSAP negative, PSA negative, cytokeratin negative; Factor VIII-related antigen positive, CD31 positive in primary prostate tumour	Details of treatment not available to author	Details of outcome not available to author

Humphrey, [41] reported a 67-year-old man who presented with urinary tract obstructive symptoms 7 years after he had undergone radiotherapy for adenocarcinoma of the prostate gland. He underwent trans-urethral resection of prostate (TURP) which was followed by pelvic exenteration. Macroscopic examination of the specimen revealed that the prostate gland had been replaced by a 7.5 cm haemorrhagic mass which had extended into the urinary bladder. Histological examination of the specimen did show a neoplastic spindle proliferation which had formed irregular vascular channels that had dissected through the stroma of the prostate gland and the urinary bladder. Other areas of the tumour were noted to be more solid and admixed with the vascular spaces. The channels were observed to be lined by neoplastic endothelial cells which had displayed nuclear atypia. Immunohistochemical staining of the tumour had showed that the tumour cells were positively stained for CD31, CD34, and Factor VIII-related antigen. Immunohistochemistry of the tumour had also shown negative staining for pan-cytokeratin, prostate specific antigen and prostate specific acid phosphatase which confirmed that there was no residual adenocarcinoma of the prostate and that the endothelial spindle cell endothelial tumour was indeed angiosarcoma of the prostate gland. Humphrey [41] stated the following: Exposure to radiation had been linked to sarcomas of the prostate but upon taking into consideration the frequency of radiotherapy, these cases of post-irradiation sarcomas of the prostate are rare, with only few cases reported [42]; A post-irradiation (post-radiotherapy) sarcoma may be designated as such if the sarcoma develops in the irradiated field, and there is histological establishment of the diagnosis of sarcoma, a latency of at least 3 years between the radiotherapy (irradiation) and the appearance of the tumour, and documentation that the sarcoma had occurred in tissue which was normal before the radiotherapy. Majority of cases of post-irradiation sarcoma of the prostate gland that had been reported in the literature were diagnosed after radiotherapy for carcinoma of the prostate gland and in their opinion should not formally be considered post-irradiation sarcoma in view of the fact that the sarcoma developed in prostatic tissue that was not normal, having been previously involved with adenocarcinoma. It would be argued that the suggestion of Humphrey [41] that the terminology of post-irradiation sarcoma of the prostate gland should not be used because the prostate gland which had been irradiated had been afflicted by disease prior to the irradiation was not a normal prostate is not absolutely correct. The reason is that when biopsies of the prostate gland that had been afflicted by adenocarcinoma of the prostate gland are taken histological examination tends to show various percentage areas of the prostate that have tumor tissue and areas of the prostate that are normal. There is a likelihood that the sarcomas had developed from cells in the prostate gland that were normal. It is only if the sarcoma is shown to have arisen from a cell that had been affected by adenocarcinoma that the suggestion of Humphrey [41] would be correct. What is important in cases of angiosarcomas of the prostate gland or other types of sarcoma of the prostate gland is for clinicians to obtain permission from their patients to undertake genetic studies to show whether there had been mutation of TP53 tumor suppressor gene or any other gene that could be attributed to the radiotherapy and to search for treatment modalities that would improve prognosis of PASOP. Considering the fact that biopsies of the prostate gland or trans-urethral resection of the prostate gland afflicted by PASOP may be associated with excessive bleeding the role of embolization to stop post biopsy bleeding and post trans-urethral resection of prostate excessive bleeding would need to be encouraged. Furthermore, considering the fact that some patients with PASOP may have large tumors which may prove difficult to surgically excise completely with clear margin, there is the need to develop treatment strategies on global study trials with the aim of reducing the mass of PASOP to make it possible to completely achieve complete local resection. With regard to the aforementioned aim, the role of the newly developing nanotechnology with particular reference to electroporation would need to be considered. It may be that by subjecting a patient with a histologically proven PASOP to electroporation of the prostatic disease the tumor may significantly reduce in size or the tumor may be successfully treated without the need to undergo any surgical operation. This assumption is only conjectural because to the knowledge of the author electroporation has never been used as a treatment option in the treatment of PASOP.

Gupta et al. [43] reported a case of angiosarcoma of the prostate gland in a 71-year-old man who had presented with lower urinary tract symptoms and visible hematuria 5 years after he had been treated by means of

brachytherapy for adenocarcinoma of the prostate gland. Five years prior to his presentation he had a routine serum PSA which was recorded as 4.0 ng/ml. He had biopsy of prostate and histological examination of the specimen had revealed Gleason 3+3 = 6 adenocarcinoma of the prostate for which he was treated by means of brachytherapy and following this his serum PSA became undetectable. During his recent admission, his rectal examination revealed an enlarged prostate. He had a CT urogram which had revealed a 6.1 cm x 5.3 cm partially necrotic mass which had involved the right postero-lateral aspect of the urinary bladder and this had extended into the perivesical and right iliac lymph nodes. He had urodynamic assessment which had demonstrated bladder outflow obstruction. He had cystoscopy and biopsy of the mass which had involved the bladder neck and the prostatic urethra and histological examination of this had confirmed angiosarcoma of the prostate. The histological examination of the specimen showed benign duct epithelium and undifferentiated spindled prostatic angiosarcoma and immunohistochemistry of the tumor showed strong and diffuse staining for FLI-1,CD31CD117, it also showed negative staining for CD34, various keratins (OSCAR, keratin AE1/AE3, CAM 5.2, 7, 20, and 34betaE12), PSA, prostatic acid phosphatase, actin, desmin, and thyroid transcription factor. He underwent radical cystoprostatectomy, pelvic lymph adenectomy and construction of ileal loop urinary diversion. Histological examination of the specimen showed grade 4/4 angiosarcoma with epithelioid features and that the tumor had involved the anterior and right lateral wall and trigone of the urinary bladder, the right seminal vesicle and the entire prostate. Metastatic angiosarcoma had also involved the obturator and hypogastric lymph nodes. He had PET scan which did not show any evidence of distant metastasis. He had received 3 different chemotherapy regimens but there continued to be progression of the disease in the pelvic lymph nodes. (He had paraclitaxel in the first instance (3 cycles), doxorubicin in the second instance (3 cycles), and ifosfamide in the third instance. The patient was alive at the time of the report of his case. Gupta et al. [43] stated the following:

- Even though adenocarcinoma of the prostate is very common in men only a handful of cases of angiosarcoma of the prostate have been reported in the literature.
- Prior radiotherapy for adenocarcinoma of the prostate gland had been postulated to be a risk factor for angiosarcoma.
- In view of the increasing practice of screening for prostate cancer and the use of radiotherapy in the management of adenocarcinoma of the prostate there is the likelihood that this would lead to the development of more cases of angiosarcoma of the prostate gland.
- Diagnosis of angiosarcoma of the prostate gland is made by tissue sampling (histological examination of tissues obtained from the prostate gland).
- The optimal management of these aggressive angiosarcomas of the prostate remains to be defined and the outcomes tend to be poor with a-high 1-year mortality.
- Primary care physicians and urologists should be aware of this rare entity of primary angiosarcoma of the prostate gland and refer these patients to Specialist Centers where cases of PASOP can be managed by a multi-disciplinary team.

The etiology / pathogenesis of PASOP may not be completely understood but it is likely that there are multi-factorial elements to the development of PASOP. It is likely that some PASOPS develop de novo and other PASOPS may develop through mutation of TP53 tumor suppressor gene or other genes. Whether radiotherapy does induce genetic changes including mutations and deletions pursuant to treatment for prostate cancer would need to be proven through a global multi-center study. Nevertheless, the postulate that there is the likelihood that radiotherapy induced angiosarcoma of the prostate gland does occur cannot be discounted taking into consideration the fact that in 6 cases out of 14 reported cases of PASOP a clear history of prior radiotherapy to the prostate gland had been documented and the latency period in each case has been more than 3 years. Less than 20 (about 17) cases of PASOP have so far been reported but detailed information on four more cases was not available see table 1).

Scharpira et al. [44] in 1963 reported a case of angiosarcoma of the prostate gland but the details are not available. Wick et al. [45] in 1989, reported two patients, one aged 63 years and the other 69 years. One of the patients had osseous metastasis which was treated by means of radiotherapy and diethylstilbestrol but the

treatment was not successful. The second patient was free of disease 15 months after he had undergone radical prostatectomy. Wick et al. [45] also reported that both tumors did contain a mixture of carcinoma and sarcoma and that the first patient's tumor had displayed foci of chondrosarcoma, osteosarcoma, and leiomyosarcoma but the second patient's tumor on the other hand, exhibited areas of chondrosarcoma, osteosarcoma, rhabdomyosarcoma, and angiosarcoma. The tumors on immunohistochemical staining showed positive staining for vimentin, S-100 protein, desmin, actin, myoglobin, Ulex europaeus 1 agglutinin. Whilst the sarcomatous elements were negatively stained for prostate-specific antigen, epithelial membrane antigen, and cytokeratin, the carcinomatous elements of the tumors were positively stained for prostate-specific antigen, epithelial membrane antigen and cytokeratin. Considering the fact that the second case of carcinosarcoma which contained angiosarcoma also contained other types of sarcoma as well as carcinoma components in the tumor one cannot predict which element of the mixed tumor would be most predominant in the determination of the outcome of the patient.

Russo et al. [46] reported 1 case of angiosarcoma of the prostate gland out of 43 adult soft tissue sarcomas that had been admitted to the Memorial Sloan Kettering Cancer Center (MSKCC) between July 1982 and December 1989. The details of the cases are not separately available to the author.

Luque Barona et al. [47] reported 2 patients who were aged 71 years and 78 years respectively who were diagnosed as having carcinosarcoma of the prostate gland. They reported that the primary tumor of the prostate gland in the first case was composed of adenocarcinoma which was admixed with a neoplastic mesenchymal component which had displayed foci of chondrosarcoma, rhabdomyosarcoma, and angiosarcoma. With regard to the second case, the adenocarcinoma was admixed with spindle cell carcinoma and chondrosarcoma. Both of the patients died of their disease at 3 months and 9 months respectively after surgery. Details of the two cases reported are not available to the author therefore it is not clear whether any of the patients had previously had radiotherapy or not.

Boucher et al. [48] reported the cytological features of 15 cases of angiosarcomas from various sites and among these cases, one case (a 79-year-old man) had represented a cervical lymph node metastasis from a primary prostatic epithelioid angiosarcoma. Histological examination of the primary prostatic tumor showed low-grade epithelioid angiosarcoma of the prostate and histological examination of the cervical lymph node also showed low-grade epithelioid angiosarcoma. Immunohistochemical studies showed negative staining for prostate-specific acid phosphatase (PSAP), prostate specific antigen (PSA) and cytokeratin; and factor VIII-related antigen was positive as well as CD31 was positive in the primary tumor. Details of the case including exposure to radiotherapy are not available to the author.

4. CONCLUSIONS

Primary angiosarcoma of the prostate gland (PASOP) is a rare aggressive tumor which can afflict children and adults. Less than 20 cases of PASOP have so far been reported. It has been postulated that prior radiotherapy for adenocarcinoma of the prostate gland is a risk factor for the development of PASOP. In view of the few reported cases of PASOP the true biological behavior of the tumor may not be well known and it would appear that there is no consensus opinion on the best treatment options that would improve the outcome of PASOP. In view of the increased practice of screening for adenocarcinoma of prostate and the increasing use of radiotherapy as treatment of curative intent for adenocarcinoma of the prostate gland there is the likelihood that there would in the future be an increase in the number of reported cases of PASOP provided clinicians repeat biopsies of prostate glands in patients whose diseases have relapsed after radiotherapy of their prostate glands. A global multi-Centre-trial is needed to find treatment options that would improve the prognosis of PASOP

CONSENT

Copy right permission was granted by the Archives of Pathology and Laboratory Medicine for single use reproduction of the figures and the American College of Pathologists retains the copy right to the figures.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

To Archives of Pathology and Laboratory Medicine for granting the author copy right permission to reproduce figures from their journal as stated in the article.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Arora K. In: Prostate - Other malignancies angiosarcoma pathology outlines; 2012. Available:www.pathologyoutlines.com/topic/prostteangiosarcoma.html
2. Cahan WG, Woodard HQ, Higginbotham NL, Stewart FW, Coley BL. Sarcoma arising in irradiated bone; report of 11 cases. Cancer. 1948;1(1):3-29.
3. Khaliq W, Meyer CF, Uzoaru I, Wolf RM, Antonarakis ES. Prostate angiosarcoma: Is there any association with previous radiation therapy? B. JUI. 2012;110(11): E819–E825. DOI:10.1111/j.1464-410x2012.11202xE819
4. Chen KT, Hoffman KD, Hendricks EJ. Angiosarcoma following therapeutic irradiation. Cancer. 1979;44(6):2044-2048.
5. Nanus DM, Kelsen D, Clark DG. Radiation-induced angiosarcoma. Cancer. 1987;60(4):777-779.
6. Navon JD, Rahimzadeh M, Wong AK, Carpenter PM, Ahlering TE. Angiosarcoma of the bladder after therapeutic irradiation for prostate cancer. J Urol. 1997;157(4): 1359-160.
7. Chandan VS, Wolsh L. Postirradiation angiosarcoma of the prostate. Arch Pathol Lab Med. 2003;127(7):876–878.
8. Guo CC, Pisters LL, Troncoso P. Prostate cancer invading the rectum: A clinicopathological study of 18 cases. Pathology. 2009;41(6):539-543.
9. Khaliq W, Meyer CF, Uzoaru I, Wolf RM, Antonarakis ES. Prostate angiosarcoma: A case report and literature review. Med Oncol. 2012;29(4):2901–2903. DOI: 10.1007/s12032-012-0188-x
10. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. Cancer. 2001;92(1):172-180.
11. Virtanen A, Pukkala E, Auvinen A. Angiosarcoma after radiotherapy: a cohort study of 332,163 Finnish cancer patients. Br J Cancer. 2007;97(1):115-117.
12. Kim MK, Huh SJ, Kim DY, Yang JH, Han J, Ahn YC, Lim DH. Secondary angiosarcoma following irradiation: Case report and review of the literature. Radiat Med. 1998;16(1):55-60.
13. Moon K, Stukenborg GJ, Keim J. Theodorescu D. Cancer incidence after localized therapy for prostate cancer. Cancer. 2006;107(5):991-998.
14. Bagchi Sanjeet. Genetic drivers of angiosarcoma discovered. The Lancet; 2014. Available:www.thelancet.com> lanone 2014 May 15.
15. Smith DM, Manivel C, Kapps D. Uecker angiosarcoma of the prostate: Report of 2 cases and review of the literature. J. Urol. 1986;135(2):382-384.
16. Bolesco M. Sarcome primitive de la prostate chez un enfant des deux ans et neuf mois. Bull Mem Soc Chir Bucarest. 1902;5:77
17. Salleras J, Vilar G. Considerationes a proposito de un sarcoma primitive de la prostate en un sujeto de 32 anos prostatectomia perineal. Semana Med Buenos Aires. 1924;31:1275-1279.
18. Chan GW. Angiosarcoma of the prostate: An immunohistochemical study of a case. Pathology. 1990;22(2):108–110.
19. Oliva Encina J, Gil Martinez P, Allepuz Losa C, Andrez Lazaro V, Rioja Sanz LA. Prostatic angiosarcoma: Report of a new case [in Spanish] Actas Urol. Esp. 2001; 25(1):78-80.
20. Lee HM, Song SY, Park JO, Kim BH. Primary immature teratoma of the prostate with angiosarcoma component: its unusual response to chemotherapy. Int J Urol. 2006;13(3):305-307.
21. Fury MG, Antonescu CR, Van Zee KJ, Brennan MF, Maki RG. A 14-year retrospective review of angiosarcoma: Clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. Cancer J. 2005;11(3):241-247.
22. Fayette J, Martin E, Piperno-Neumann S, et al. Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. Ann Oncol. 2007; 18(12):2030-2036.

23. Pawlik TM, Pauling AF, Mcginn CJ, Baker LH, Cohen DS, Morris JS, Rees R, Sondak VK. Cutaneous angiosarcoma of the scalp: A multidisciplinary approach. Cancer. 2003;98(8):1716-1726.
24. Lahat G, Dhuka AR, Lahat S, Smith KD, Pollock RE, Hunt KK, Ravi V, Lazar AJ, Lev D. Outcome of locally recurrent and metastatic angiosarcoma. Ann Surg. Oncol. 2009;16(9):2502–2559.
DOI: 10.1245/s10434-009-0569-3
25. Naka N, Ohsawa M, Tomita Y, Kanno H, Uchida A, Myoui A, Aozasa K. Prognostic factors in angiosarcoma: a multivariate analysis of 55 cases. J Surg Oncol. 1996; 61(3):170-176.
26. Ferrari S, Smeland S, Mercuri M, Bertoni F, Longhi A, Ruggieri P, Alvegard TA, Picci P, Capanna R, Bernini G, Müller C, Tienghi A, Wiebe T, Comandone A, Böhling T, Del Prever AB, Brösjo O, Bacci G, Saeter G, Italian and Scandinavian groups. Neoadjuvant chemotherapy with high-dose ifosfamide, high-dose methotrexate, cisplatin, and doxorubicin for patients with localized osteosarcoma of the extremity: A joint study by the Italian and Scandinavian Sarcoma Groups. J Clin Oncol. 2005;23(34):8845-8852.
27. Pervaiz N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer. 2008;113(3):573-581.
28. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. Lancet Oncol. 2010;11(10):983-991.
DOI: 10.1016/S1470-2045(10)70023-1
29. Mocellin S, Rossi CR, Brandes A, Nitti D. Adult soft tissue sarcomas: Conventional therapies and molecularly targeted approaches. Cancer Treat Rev. 2006; 32(1):9-27.
30. Verweij J, Lee SM, Ruka W, Buesa J, Coleman R, van Hoessel R, Seynaeve C, di Paola ED, van Glabebeke M, Tonelli D, Judson IR. Randomized phase II study of docetaxel versus doxorubicin in first- and second-line chemotherapy for locally advanced or metastatic soft tissue sarcomas in adults: A study of the European organization for research and treatment of cancer Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 2000;18(10):2081-2086.
31. Penel N, Bui BN, Bay JO, Cupissol D, Ray-Coquard I, Piperno-Neumann S, Kerbrat P, Fournier C, Taieb S, Jimenez M, Isambert N, Peyrade F, Chevreau C, Bompas F, Brain EG, Blay JY. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: The ANGIOTAX study. J Clin Oncol. 2008;26(32):5269-5274.
DOI: 10.1200/JCO.2008.17.3146
32. Raina V, Sengar M, Snukla NK, Deo SS, Mohanty BK, Sharma D, Ray R, Das P, Rath GK. Complete response from the thalidomide in angiosarcoma after treatment of breast cancer. J Clin Oncol. 2007;25(7):900-901.
DOI: 10.1200/JCO.2006.09.7261
33. Koontz BF, Miles EF, Rubio MA, Madden JF, Fisher SR, Scher RL, Brizel DM. Preoperative radiotherapy and bevacizumab for angiosarcoma or the head and neck: Two case studies. Head Neck. 2008;30(2):262-266.
34. Taylor KL, Oates RK, Grane R, Leaman DW, Borden EC, Linder EC, Lindner DJ. IFNalpha1, 8 inhibits tumor-induced angiogenesis in murine angiosarcomas. J Interferon Cytokine Res. 2006; 26(5):353-361.
35. Maki RG, D'Adamo DR, Keohan ML, Saulle M, Schuetze SM, Undevia SD, Livingston MB, Cooney MM, Hensley ML, Mita MM, Takimoto CH, Kraft AS, Elias AD, Brockstein B, Blachère NE, Edgar MA, Schwartz LH, Qin LX, Antonescu CR, Schwartz GK. Phase II study of sorafenib in patients with metatastatic or recurrent sarcomas. J Clin Oncol. 2009;27(19): 3183–3140.
DOI: 10.1200/JCO.2008.20.4495
36. Burns BT, Blakey SA, Hams WB. Complete response of metastatic angiosarcoma to liposomal doxorubicin and interferon-22a. Proc Am Soc Clin Oncol. 2002;21:29339 (abstr).
37. Ohguri T, Imada H, Nomoto S, Yahara K, Hisaoka M, Hashimoto H, Tokura Y, Nakamura K, Shioyama Y, Honda H, Terashima H, Mproi Y, Furue M, Korogi Y. Angiosarcoma of the scalp treated with curative radiotherapy plus recombinant interleukin-2 immunotherapy. Int J Radiat Oncol Biol Phys. 2005;61(5):1446-1453.
38. Mark RJ, Poen JC, Tran LM, Fu YS, Juillard GF. Angiosarcoma. A report of 67 patients and a review of the literature. Cancer. 1996;77(11):2400-2406.

39. Cafiero F, Gipponi M, Peressini A, Queirolo P, Bertoglio S, Comandini V, Percivale P, Sertoli M R, Badellino F. Radiation-associated angiosarcoma: Diagnostic and therapeutic implications: Two case reports and a review of the literature. Cancer.1996;77(12):2496-2502.
40. Campschroer T, van der Kwast TH, Jonges GN, Lock MTWT. Angiosarcoma of the prostate: A more frequent finding in the future owing to radiotherapy? A literature review with treatment implications based on a case report Scandinavian Journal of Urology. 2014;48(5):420-425.
DOI: 10.3109/21681805.2014.905632
41. Humphrey PA. Angiosarcoma of the prostate J Urol. 2012;187(2):684-685.
DOI: 10.1016/juro.2011.11.007
42. Humphrey PA. Prostate Pathology Chicago ASCP Press. 2003;440-441.
43. Gupta M, Patnaik MM, Naina HV. Angiosarcoma of the prostate gland following brachytherapy for adeno-carcinoma. Current Urology. 2014;8(2): 109-112.
44. Scharpira HB. Case no. 208. angiosarcoma of the prostate. J Mt Sinai Hosp N Y. 1963;281-283.
45. Wick MR, Young RH, Malvesta R, Beebe DS, Hansen JJ, Dehner LP. Prostate carcinosarcomas. Clinical, histologic, and immunohistochemical data on two cases. Am J Clin Pathol. 1989;92(2):131-139.
46. Russo P, Brady MS, Conlon K, Hajdu SI, Fair WR, Herr HW, Brennan MF. Adult urological sarcoma. J Urol. 1992; 147(4):1032-1036:Discussion 1036-1037.
47. Luque Barona R, Gonzalez Campora, Vicioso Recio L, Requena Tapias MJ, Lopez Beltran A. Synchronous prostatic carcinosarcoma: Report of 2 cases and review of the literature. Actas Urol. Esp. 2000;24(2):173-178.
48. Boucher LD, Swanson PE, Stanley MW, Silverman JF, Raab SS, Geisinger KR. Cytology of angiosarcoma findings in fourteen aspiration biopsy specimens and one pleural fluid specimen. Am J Clin Pathol. 2000;114(2):210-219.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/12629