

Adrenal adenomatoid tumor in a patient with human immunodeficiency virus

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Introduction

Adenomatoid tumors most commonly occur in the genital tract including the epididymis, uterus, or fallopian tube.¹ Interestingly, these tumors have also been reported to occur in the adrenal gland.¹⁻⁶ Adrenal adenomatoid tumors are derived from mesothelial cells from mesothelial rests within the adrenal gland. These rests are likely present due to the close embryological relationship between the adrenal glands and the Mullerian tract.⁶⁻⁷ This report represents the 29th case of an adrenal adenomatoid tumor in the literature, but is only the second case described in a patient with human immunodeficiency virus and the first case in which positron emission tomographic scanning was used as part of the diagnostic work-up.

Abstract

We present the clinical course of a patient with human immunodeficiency virus and an adrenal adenomatoid tumor (AAT). We describe the clinical course and laboratory, radiographic, and microscopic findings of a patient with human immunodeficiency virus (HIV) and an adenomatoid tumor of the right adrenal gland. A review of the literature was also done via electronic searches through PubMed for articles from 1965 to 2008 that contained the following search terms, *adenomatoid tumor* limited to the English language only. A 22 year-old African-American male with HIV was incidentally found to have a hypermetabolic right adrenal mass. The patient underwent laparoscopic adrenalectomy and the mass had morphological and immunohistochemical features that were consistent with an AAT. A review of the medical literature reveals that almost all cases of AAT were in male patients (96%) with a mean age of 41±11 years (range=22-64) with no significant difference in laterality (right side=46%, left side=50%, unknown=4%). AAT have an average size of 4.2±3.5 cm (range=0.5-14.3 cm). Pre-operative imaging studies do not appear to be able to reliably distinguish AAT from other types of adrenocortical tumors. For reasons that require further research, AAT typically occur in male patients and may be associated with immunosuppression. AAT can be safely removed laparoscopically with no evidence of long-term recurrence even with tumor extension beyond the adrenal capsule.

Materials and Methods

We describe the clinical course, laboratory, radiographic, and microscopic findings of a patient with human immunodeficiency virus and an adenomatoid tumor of the right adrenal gland. A review of the literature was also done via electronic searches through PubMed for articles from 1965 to 2008 that contained the following search terms, *adenomatoid tumor* limited to the English language only. All articles that contained reported cases of adenomatoid tumor were analyzed. Pertinent references from these articles were reviewed and synthesized. This cycle continued until it was felt that a complete listing of all published cases of adenomatoid tumors in the English language was obtained. This study was approved by the Institutional Review Board at University Hospitals of Cleveland.

Results

Report of a case

AH is a 22 year-old African-American male with a past medical history of human immunodeficiency virus on HAART (Highly Active Anti-Retroviral Therapy) who was noted to have an incidental adrenal mass on computed tomography of the chest done as a follow-up study for mediastinal lymphadenopathy. No previous adrenal masses were noted on previous computed tomographic imaging.

The patient denied any symptoms of palpitations, diaphoresis, flushing, or uncontrolled high blood pressure. He subsequently had a magnetic resonance imaging scan to

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Key words: adenomatoid tumor, adrenal, human immunodeficiency virus.

Conflict of interest: the authors report no conflicts of interest.

Received for publication: 8 March 2011.

Accepted for publication: 16 April 2011.

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Rare Tumors 2011; 3:e21
doi:10.4081/rt.2011.e21

further characterize the adrenal mass. It was a right adrenal mass that measured 2.7 by 1.6 by 2.3 cm in size with atypical enhancement patterns with gadolinium contrast. The patient underwent a complete adrenal hormonal work-up. His 24-hour urine catecholamines, serum aldosterone, and plasma renin activity were all normal. Serum cortisol level was mildly elevated, but his urinary cortisol level was normal. Prior to surgical referral, the patient also underwent a follow-up positron emission tomographic scan which demonstrated increased uptake of 3.4 SUV. Based on the above findings, the differential diagnosis included a non-functioning adrenal adenoma or malignancy. The patient underwent a laparoscopic right adrenalectomy with no post-operative complications on follow-up examination seven months later.

Pathologic findings

On gross examination, the adrenal gland was 5.5 by 3.0 by 1.0 cm in size with a well-circumscribed, firm, tan-gray cortical mass that measured 2.5 by 2.5 by 1.0 cm. No areas of necrosis or hemorrhage were identified in the mass. On light microscopy examination, the adrenal mass was composed of epithelioid cells forming nests, cords, and tubules. There were no areas of necrosis, mitotic activity, or significant atypia. On immunohistochemical examination, the cells in the adrenal mass were positive for calretinin and cytokeratins (AE1/3 and CAM 5.2) and negative for CD31, CD34, and Factor VIII. These morphological and immunohistochemical features were consistent with an adenomatoid tumor (Figures 1-3).

Literature review

As illustrated in Table 1 and 2, there have

Table 1. clinical data from review of the medical literature

#	Author	Gender	Age	Side of mass	Size of mass (cm)	Clinical data	CT Scan	MRI	U/S	Hormonal function	Resection	Follow-up
1	Evans <i>et al.</i>	MALE	36	LEFT	11	Painless hematuria	Y	N	N	All WNL	OPEN	8 months
2	Simpson <i>et al.</i>	MALE	44	LEFT	Not stated	HTN	Y	N	N	Elevated urinary homovanillic acid level	OPEN	177 months
3	Travis <i>et al.</i>	MALE	24	LEFT	1.1	Cushing syndrome	Not stated	Not stated	Not stated	Not stated	OPEN	Patient expired 6 months later secondary to massive pulmonary carcinoid metastases
4	Raaf <i>et al.</i>	MALE	49	RIGHT	1.3	Incidental	Autopsy	Autopsy	Autopsy	Autopsy	Autopsy	Found at autopsy
5	Raaf <i>et al.</i>	MALE	57	LEFT	3.8	Incidental	Autopsy	Autopsy	Autopsy	Autopsy	Autopsy	Found at autopsy
6	Raaf <i>et al.</i>	FEMALE	50	RIGHT	0.5	Incidental	Autopsy	Autopsy	Autopsy	Autopsy	Autopsy	Found at autopsy
7	Raaf <i>et al.</i>	MALE	40	LEFT	6	Incidental	Y	N	N	Not stated	Not stated	Not stated
8	Angeles-Angeles <i>et al.</i>	MALE	34	RIGHT	3	AIDS	Autopsy	Autopsy	Autopsy	Autopsy	Autopsy	Found at autopsy
9	Gasque <i>et al.</i>	MALE	28	RIGHT	9	Abdominal pain	N	Y	Y	All WNL	Not stated	16 months
10	Glatz <i>et al.</i>	MALE	54	LEFT	6.5	Sudden epigastric pain	Y	N	N	Not stated	Not stated	Not stated
11	Chung-Park <i>et al.</i>	MALE	51	RIGHT	3	HTN	Y	N	N	Low plasma renin activity and high aldosterone to plasma renin ratio	LAP	Not stated
12	Isotalo <i>et al.</i>	MALE	37	LEFT	3.1	Incidental	Not stated	Not stated	Not stated	Not stated	Not stated	40 months
13	Isotalo <i>et al.</i>	MALE	31	RIGHT	3.2	Incidental	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
14	Isotalo <i>et al.</i>	MALE	31	Not stated	3.5	Syncope	Not stated	Not stated	Not stated	Not stated	Not stated	50 months
15	Isotalo <i>et al.</i>	MALE	64	LEFT	1.2	Incidental	Autopsy	Autopsy	Autopsy	Autopsy	Autopsy	Found at autopsy
16	Kim and Ro	MALE	33	LEFT	1.7	HTN	Y	N	N	Not stated	Not stated	Not stated
17	Denicol <i>et al.</i>	MALE	42	LEFT	14.3	HTN	Y	N	Y	All WNL	OPEN	3 years
18	Garg <i>et al.</i>	MALE	46	RIGHT	11	Right flank pain	Y	N	Y	Not done	OPEN	Not stated
19	Garg <i>et al.</i>	MALE	33	LEFT	1.7	HTN	Y	N	N	Not done	OPEN	Not stated
20	Garg <i>et al.</i>	MALE	33	RIGHT	4.2	Incidental	Y	Y	N	All WNL	OPEN	1 year
21	Varkarakis <i>et al.</i>	MALE	54	RIGHT	3.6	Incidental	Y	Y	N	Elevated urinary homovanillic acid level	LAP	1 year
22	Hamamatsu <i>et al.</i>	MALE	30	LEFT	3	Incidental	Autopsy	Autopsy	Autopsy	Autopsy	Autopsy	Found at autopsy
23	Timonera <i>et al.</i>	MALE	47	RIGHT	5.6	Incidental	Y	Y	N	All WNL	LAP	Not stated
24		MALE	52	RIGHT	2	HTN	Y	Y	N	All WNL	LAP	Not stated
25	Fan <i>et al.</i>	MALE	42	LEFT	2.5	HTN	Y	N	N	All WNL	LAP	Not stated
26	Hoffman <i>et al.</i>	MALE	26	RIGHT	1.5	Incidental	Y	N	N	Not done	OPEN	Not stated
27	Bisceglia <i>et al.</i>	MALE	39	RIGHT	5.5	Incidental	Y	N	N	All WNL	OPEN	Not stated
28	Liu <i>et al.</i>	MALE	44	LEFT	16.7	Incidental	Y	N	N	All WNL	OPEN	3 months
29	Phitayakorn <i>et al.</i>	MALE	22	RIGHT	2.5	Incidental	Y	Y	N	Elevated serum cortisol	LAP	7 months

Table 2. Pathological data from review of the medical literature.

# Author	Tumor characteristics	Tumor extension	Histochemistry	Electron microscopy
1 Evans <i>et al.</i>	Tan, smooth with cystic spaces	No extension	Not stated	Numerous slender microvilli, desmosome-like intracellular junctions, intracytoplasmic tonofilaments
2 Simpson <i>et al.</i>	Fleshy, gray, solid, cystic	Extension into peri-adrenal adipose tissue	Positive for antihuman cytokeratin, but negative for carcinoembryonic antigen; No glycogen or mucin content	Not done
3 Travis <i>et al.</i>	Pale, white, and solid	Extension into cortex and perirenal adipose tissue	Strongly positive for keratin (AE1/AE3) and vimentin; Weakly positive for epithelial membrane antigen	Tortuous microvilli with a moderate amount of tonofilaments
4 Raaf <i>et al.</i>	White and solid	No extension	Reacted with MAK-6 and AE1/AE3; Positive staining for vimentin	Long, thin, bushy microvilli with well-developed desmosomes, basal laminae, and cytoplasmic tonofilaments
5 Raaf <i>et al.</i>	White, solid, firm, and smooth	No extension	Reacted with MAK-6 and AE1/AE3; Positive staining for vimentin	Not done
6 Raaf <i>et al.</i>	White, firm and smooth	No extension	Not stated	Not done
7 Raaf <i>et al.</i>	White, predominantly cystic	No extension	Reacted with MAK-6 and AE1/AE3; Positive staining for vimentin laminae, and cytoplasmic tonofilaments	Long, thin, bushy microvilli with well-developed desmosomes, basal
8 Angeles-Angeles <i>et al.</i>	Ill-defined, white-yellowish, and firm nodule	No extension	Stained positive for low molecular weight cytokeratin CKAE-3 and weakly for vimentin	Not done
9 Gasque <i>et al.</i>	Grayish with pseudocyst	No extension	Stains positive for cytokeratin (CAM 5.2)	Not done
10 Glatz <i>et al.</i>	Pale-yellow, spongy, cystic	No extension	Strongly positive for keratin (Cam 5.2, Lu-5) and calretinin; Weakly positive for thrombomodulin. Negative staining for CEA, MOC-31, BerEP4, and CD34.	Long and slender microvilli Long and slender microvilli and abundant desmosomes along luminal surface with bundles of tonofibrils in the cytoplasm
11 Chung-Park <i>et al.</i>	Pale-yellow, solid, and firm	Extension into adrenal cortex	Positive for cytokeratin and calretinin, but negative for synaptophysin, chromogranin, factor VIII, CD34, and S-100.	Long, busy microvilli with intracytoplasmic tonofilaments, and intercellular desmosomes
12 Isotalo <i>et al.</i>	Solitary and poorly circumscribed	Extension into peri-adrenal adipose tissue	Strongly positive for calretinin, cytokeratins (AE1/AE3, CAM 5.2, CK7) and vimentin. Weakly positive for CK5/CK6. Negative for CD15, CD31, CD34, CK20, MOC31, and p-CEA.	Not done
13 Isotalo <i>et al.</i>		Extension into adrenal gland capsule		Not done
14 Isotalo <i>et al.</i>		Extension into adrenal gland capsule		Not done
15 Isotalo <i>et al.</i>		Extension into peri-adrenal adipose tissue		Not done
16 Kim and Ro	Smooth, grayish, white and firm with cystic spaces	No extension	Stained positive for cytokeratin and calretinin	Desmosomes. Cytoplasmic fibrillar networks, and numerous long, bushy, microvilli on luminal surfaces
17 Denicol <i>et al.</i>	Multicystic, yellow, opaque	No extension	Stains positive for AE1, AE3, and vimentin	Not done
18 Garg <i>et al.</i>	Fibrous wall with an intramural well-demarcated tumor containing adipose tissue and lymphoid	No extension	Stains positive for calretinin and focal weak staining for cytokeratin 5/6	Numerous long, bushy, and slender microvilli
19 Garg <i>et al.</i>	Aggregates, areas of mucin production, cells with a signet ringlike appearance	No extension	Stains positive for calretinin and strong staining for cytokeratin 5/6	Numerous long, bushy, and slender microvilli
20 Garg <i>et al.</i>		No extension	Stains positive for calretinin	Not done
21 Varkarakis <i>et al.</i>	Tan nodular with sites of heterotopic ossification	No extension	Stains positive for calretinin	Not done
22 Hamamatsu <i>et al.</i>	White, solid, well-circumscribed, and smooth	No extension	Stained positive for calretinin, D2-40, vimentin, and cytokeratins (AE1/AE3, OV-TL 12/30, CAM 5.2, and MNF116)	Not done
23 Timonera <i>et al.</i>	Well-circumscribed, solid,	No extension with variegated yellow and tan cut surface	Strongly positive for D2-40 and calretinin	Not done and weak reactivity for cytokeratin 5/6
24 Timonera <i>et al.</i>	Well circumscribed, heterogeneous cystic and solid mass with hemorrhagic areas			

Table 2 continued next page.

Table 2. Continued from previous page.

# Author	Tumor characteristics	Tumor extension	Histochemistry	Electron microscopy
25 Fan <i>et al.</i>	Ill-defined edge, smooth, greyish-white, firm, with no hemorrhage or necrosis	Focal infiltration of adrenal cortex and medulla	Positive for cytokeratin 7, calretinin, vimentin, antimesothelial cell ab, and epithelial membrane antigen	Not done
26 Hoffman <i>et al.</i>	Grey-whitish pattern of small cystic nodules with trabeculae	No extension	Positive for cytokeratin and calretinin, but negative for CD31, CD34, and CD56	Not done
27 Bisceglia <i>et al.</i>	Cystic, gray to pale yellowish with slight mural thickening and short endoluminal papillations	No extension	Positive to cytokeratins and calretinin, but negative to endothelial markers	Numerous small microvilli (coelomic or mesothelial type)
28 Liu <i>et al.</i>	Ill-circumscribed multilocular cystic tumor with tan wall with no hemorrhage or necrosis, cyst fluid was clear-yellow	Enveloped around the ipsilateral renal artery and vein	Positive for calretinin and epithelial membrane antigen, but negative for endothelial markers	Not done
29 Phitayakorn <i>et al.</i>	Well circumscribed, tan-gray cortical mass	No extension	Stained positive for calretinin and cytokeratins (AE1/AE3 and CAM 5.2), and stained negative for CD31, CD34, and factor VIII.	Not done

been 29 reported cases of adenomatoid tumors of the adrenal gland in the recent English-language medical literature.¹⁻¹⁹ Almost all of these cases were in male patients (97%) with a mean age of 40 years (range=22-64). The laterality of these tumors is approximately 14 (48%) tumors on the right side and 14 (48%) tumors on the left side (laterality was unknown in one patient) with an average size of 4.6±4.0 cm (range=0.5-16.7 cm). Many of these tumors were either discovered as part of an autopsy or incidentally found as part of a diagnostic work-up for various symptoms including: painless hematuria, hypertension, abdominal pain, and Cushing's syndrome. Various imaging modalities were used including computed tomography (n=18), magnetic resonance imaging (n=6), ultrasound (n=3), and positron emission tomography (n=1). Interestingly, eight (31%) patients had adenomatoid tumors that extended into the perirenal adipose tissue or the adrenal gland capsule. However, no recurrences have been reported with a median follow-up time of 33 months (range=3 to 177 months).

In terms of tumor color, these tumors have been described as being white, tan, fleshy, pale-yellow, opaque, and grayish. In terms of tumor consistency, however, these tumors have been described as being firm, smooth, cystic, solid, and well-circumscribed. Other histopathological characteristics have been noted in adenomatoid tumors including: heterotopic ossification, lymphoid aggregates, sites of mucin production, and cells with a signet ring-like appearance.

Adenomatoid tumors have been found to stain positive with a wide variety of agents including: vimentin, calretinin, cytokeratins (CAM 5.2, CKAE1, and CKAE3), MAK-6, D2-40, OV-TL 12/30, and MNF 116. A few studies

have examined adenomatoid tumors using electron microscopy and found various features including: numerous long, thin, bushy microvilli with well developed desmosomes, basal laminae, and cytoplasmic fibrillar networks.

Discussion

Patients with human immunodeficiency virus (HIV) frequently present with a number of associated neoplasms, often as a result of their immunosuppression. It is very unusual for HIV-positive patients to present with adrenal gland neoplasms other than Kaposi's sarcoma or lymphoma. HIV-positive patients may also present with infectious etiologies that may present as an adrenal mass, including cytomegalovirus necrotizing adrenalitis, mycobacterium, cryptococcus, or

other fungal infections.^{20,21} This case represents only the second reported case of an adenomatoid tumor in a patient with HIV. However, it is unknown how many other patients with reported adrenal adenomatoid tumors were tested for HIV. It is possible

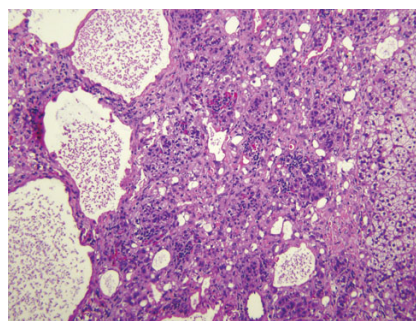


Figure 1. The tissue at far right in this image is normal adrenal cortical tissue. The native adrenal tissue is replaced or extensively infiltrated by tumor cells forming small solid nests as well as anastomosing channels and tubules of variable size and shape.

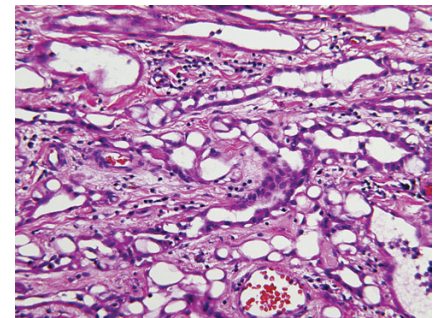


Figure 2. Lesional cells range from plump epithelioid cells to flattened cells resembling endothelial cells, and many exhibit prominent vacuolization, to an extent that may mimic a signet-ring appearance with apparent intracytoplasmic lumina. They do not exhibit nuclear pleomorphism, necrosis or mitotic activity.

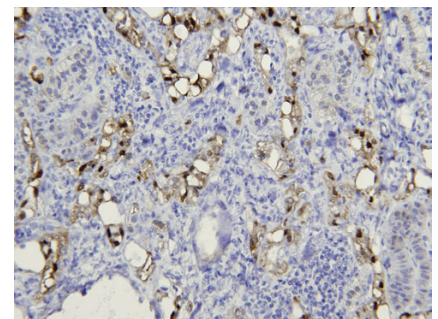


Figure 3. Immunostain for calretinin highlights the tumor cells, in keeping with their mesothelial derivation.

that the incidence of adrenal adenomatoid tumors in patients with HIV may increase as a consequence of anti-retroviral therapies or chronic immunosuppression.

Although the first adenomatoid tumor was described in 1945, adrenal adenomatoid tumors were not well described until the late 1980's.²² This result may be due to the increasing use of diagnostic computed tomographic imaging in detecting adrenal *incidentalomas*. This case also highlights an important caveat in that imaging techniques such as computed tomography cannot reliably distinguish adrenal adenomatoid tumors from other adrenocortical tumors.⁵ Magnetic resonance imaging of the adrenal adenomatoid tumor in this patient was more consistent with a functional adrenal tumor. Another study that used MRI in a patient with an adrenal adenomatoid noted that the tumor was mainly solid with cystic peripheral portions, and that the solid areas were homogeneously isointense to the spleen on all images.⁵ In this particular case, the use of a positron-emission tomographic (PET) scan was also not helpful in pre-operatively diagnosing an adrenal adenomatoid tumor. In fact, the level of 18F-FDG uptake of 3.4 SUV was in the range of malignant adrenal lesions.²³

Finally, this case emphasizes that although adrenal adenomatoid tumors have been described in the past as extending into the perirenal adipose tissue, the clinical behavior is definitely benign.¹⁰ Adrenal adenomatoid tumors may be misclassified as lymphangiomas or adenocarcinomas because of infiltrative borders into the adrenal capsule or periadrenal adipose tissue.²⁴ These tumors can be reliably distinguished from adrenal adenocarcinoma as adenomatoid tumors stain positive for keratin and do not produce mucin. Based on Table 1, local resection limited to the adrenal gland itself without any specific post-operative surveillance protocol appears to be sufficient treatment of adrenal adenomatoid tumors. Laparoscopic adrenalectomy which is the current gold-standard for the surgical resection of adrenal tumors can be safely employed in the case of adrenal adenomatoid tumors.

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