Gynecologic Oncology Reports 17 (2016) 96–98

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case series

Renal transplantation-related risk factors for the development of uterine adenomatoid tumors

Teruyuki Mizutani [a,*], Osamu Yamamuro [a], Noriko Kato [a], Kazumasa Hayashi [a], Junya Chaya [a], Norihiko Goto [b], Toyonori Tsuzuki [c]

[a] Department of Obstetrics and Gynecology, Nagoya Daini Red Cross Hospital, Nagoya, Japan
[b] Department of Transplant Surgery, Nagoya Daini Red Cross Hospital, Nagoya, Japan
[c] Department of Pathology, Nagoya Daini Red Cross Hospital, Nagoya, Japan

ARTICLE INFO

Article history:
Received 16 December 2015
Received in revised form 29 April 2016
Accepted 8 May 2016
Available online 11 May 2016

Keywords:
Uterine
Benign tumors
Adenomatoid tumors
Renal transplantation
Immunosuppression
Dialysis

1. Introduction

The term adenomatoid tumor (AT) was introduced by Golden and Ash (Golden and Ash, 1945) to describe a tumor with distinct morphologic features resembling an adenoma but having obscure histogenesis. Currently, ATs are considered to be specialized benign mesothelial tumors, (Ferenczy et al., 1972; Taxy et al., 1974) usually found in the genital systems of both males and females, and only rarely reported in other sites such as the adrenal gland and peritoneum (Craig and Hart, 1979).With respect to uterine ATs, although three such ATs have been reported as occurring in renal transplant recipients under immunosuppression therapy, (Bülent Tiras et al., 2000; Cheng and Wee, 2003) there has been no report suggesting that AT might occur frequently in renal transplant recipients under immunosuppression therapy.

2. Materials and methods

We conducted a retrospective study of all patients who underwent total hysterectomy (all types, such as simple total hysterectomy, modified radical hysterectomy, and radical hysterectomy) at Nagoya Daini Red Cross Hospital during April 2003 through March 2011. All of the removed specimen materials were diagnosed by a pathologist. The epidemiologic and clinical manifestations of uterine ATs from immunosuppressed renal transplant recipients were analyzed.

This work was reviewed and approved by the Institutional Review Board of Nagoya Daini Red Cross Hospital. Informed consent was obtained from all patients.

Data were analyzed using SPSS version 21.0 (IBM, Armonk, NY, USA). Comparisons were assessed by the Fisher's exact test and the Mann-Whitney *U* test. The level of significance was selected at $P < 0.05$.

3. Results

There were 1094 total hysterectomies performed during the study period. Uterine ATs (Figs. 1 and 2) were found in 17 (1.55%) of the 1094 reviewed cases. Among the 17 patients (median age, 46 years; age range, 24–73 years) with uterine ATs, 10 (58.8%) were immunosuppressed renal transplant recipients (Table 1). The other seven patients had no special medical history. Of the 17 cases of uterine AT, irregular menses was the main complaint in seven (41%), whereas three (18%) patients had reported hypermenorrhea, two (12%) had suffered dysmenorrhea, and two (12%) had asymptomatic swelling. Other patients had urinary retention or no symptoms, and in one patient, the AT was accidentally discovered via Porro's operation. Preoperatively, 12 patients were diagnosed with uterine leiomyomas, two with endometrial cancer, one with endometrial hyperplasia, one with pseudoaneurysm of the uterine artery, and one with ovarian cancer. None of the 1094 patients who underwent total hysterectomy were infected with human immunodeficiency virus (HIV). Moreover, none of the patients were diagnosed preoperatively with AT; all of the ATs were found in the hysterectomy specimens after surgery. It was difficult to investigate internal medication use among all patients.

Of the 1094 hysterectomy patients, 14 (1.28%) were immunosuppressed renal transplant recipients. Of these 14 immunosuppressed renal transplant recipients, 10 (71.4%) had uterine ATs, which were found in the hysterectomy specimens after surgery. A significant difference was observed between occurrence and non-occurrence of AT in the renal transplant recipients ($P < 0.001$). The four renal transplant recipients without uterine ATs had undergone hysterectomy for uterine leiomyomas, cervical cancer, endometrial cancer, and hematometra

* Corresponding author at: Department of Obstetrics and Gynecology, Nagoya Daini Red Cross Hospital, 2-9 Myouken-chou, Shouwa-ku, Nagoya, Aichi 466-8650, Japan.
E-mail address: teruyuki@nagoya2.jrc.or.jp (T. Mizutani).

http://dx.doi.org/10.1016/j.gore.2016.05.003

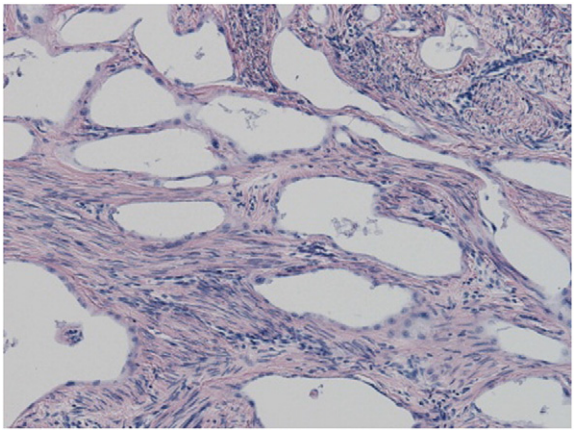

Fig. 1. Microscopic findings of adenomatoid tumor. Microscopically, the tumor is composed of ramifying tubular, cystic spaces made by non-atypical mesothelial-like cells between smooth muscle cells. These spaces are lined by cuboidal or flattened cells.

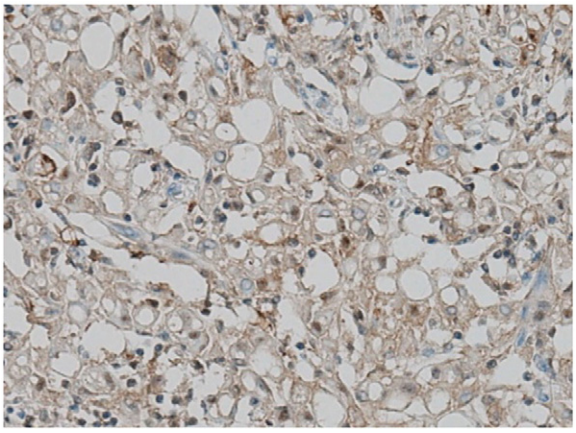

Fig. 2. Immunostain of adenomatoid tumor. Tubular formations lined by flattened cells are immunopositive for calretinin.

(Table 2). No differences regarding the medications were evident between the patients. All of the patients who received renal transplants had experienced onset of renal failure. In the 10 patients with AT, the causes of their renal failure were chronic glomerulonephritis (four patients), IgA nephropathy (three patients), pregnancy complication (one patient), membranoproliferative glomerulonephritis (one patient), and nephrotic syndrome (one patient). The causes of renal failure in the four patients without AT were IgA nephropathy, nephrosclerosis, thrombotic thrombocytopenic purpura, and unknown origin.

The median length of time each of the 14 renal transplant recipients who had been undergoing dialysis and the median duration from transplantation to hysterectomy. The 10 AT patients had received maintenance dialysis ranging in vintage from 7 to 172 months (median, 43 months) until undergoing kidney transplantation. Only one patient underwent temporary peritoneal dialysis. The four renal transplant recipients without AT had received hemodialysis ranging from 3 to 27 months (median vintage, 10.5 years). The occurrence of AT was significantly increased by the length of time on dialysis ($P < 0.047$).

In the 10 renal transplant recipients with AT, the duration between their kidney transplant surgery and hysterectomy ranged from 67 to 284 months (median, 142.5 months). In the four renal transplant recipients without AT, the duration between their kidney transplant operation and hysterectomy ranged from 39 to 250 months (median, 62.5 months).

4. Discussion

Adenomatoid tumors of the uterus are benign, rare lesions of the female genital tract. Their actual incidence may be higher than the recorded incidence because they are not usually biopsied due to their leiomyoma-like appearance and small size (Bülent Tiras et al., 2000). The incidence of adenomatoid tumors in the uterus has been reported as between 0.1% and 1% (Tiltman, 1980). Although some cases of AT have been discovered preoperatively as large multicystic tumors, (De Rosa et al., 1992; Nogales et al., 2002) AT is difficult to discover preoperatively. In the present study, all cases of AT were incidental findings in hysterectomy specimens. One patient (5.88%) had a large cystic tumor (Fig. 3) with a diameter of 10 cm; the other 16 patients had small, solid tumors.

The rate of AT in this study (1.55%) was higher than that in previous studies (Tiltman, 1980). The reason could be that immunosuppressed renal transplant recipients have a predisposition for AT. In the present study, the rate of AT in the patients who were not immunosuppressed renal transplant recipients (0.65%) was the same as that in previous studies.

When we found that AT occurred frequently in renal transplant recipients under immunosuppression therapy, the first cause that came to mind was peritoneal dialysis. The mesothelium cells leak to the intraperitoneal spaces during peritoneal dialysis, (JSDT (The Japanese Society for Dialysis Therapy), 2009) and it is suggested that AT is generated from the mesothelium (Ferenczy et al., 1972; Taxy et al., 1974). We therefore conjectured that the cause could be attributed to peritoneal dialysis. However, among the patients of the present study, there was

Table 1
Characteristics of renal transplant recipients with adenomatoid tumor (AT).

Age at operation (y)	Age at dialysis (y)	Age at transplant (y)	Obstetrical status	Medicines	Presenting symptom	Original disease	Preoperative diagnosis
40	27 36[a]	27	Nulligravida	Unknown	Irregular menses	Chronic glomerulonephritis	Myoma
44	30	30	Parturition 1	PSL Cys MZ	Hypermenorrhea	Chronic glomerulonephritis	Myoma
44	33	34	Nulligravida	PSL Cys MMF	Irregular menses	Membranoproliferative glomerulonephritis	Myoma
44	24	32	Nulligravida	PSL Cys MZ	Irregular menses	Chronic glomerulonephritis	Endometrial cancer
46	25	29 38[b]	Parturition 2	PSL Cys	Urinary retention	Pregnancy nephropathy	Myoma
24	8[c]	11	Nulligravida	PSL TAC	Dysmenorrhea	Nephrotic syndrome	Myoma
58	28	34	Parturition 1	PSL Cys MZ	Irregular menses	Chronic glomerulonephritis	Endometrial hyperplasia
52	38	40	Nulligravida	PSL TAC	No symptoms	IgA nephropathy	Myoma
41	30	36	Nulligravida	PSL Cys MMF	Hypermenorrhea	IgA nephropathy	Myoma
47	33	35	Nulligravida	PSL Cys MMF	Irregular menses	IgA nephropathy	Myoma

PSL, prednisolone; Cys, cyclosporine; MZ, mizoribine; MMF, mycophenolate mofetil; TAC, tacrolimus.
[a] Renal function deteriorated after kidney transplantation, and patient received hemodialysis again.
[b] Renal function deteriorated after kidney transplantation, and patient underwent transplantation again.
[c] Peritoneal dialysis.

Table 2
Characteristics of renal transplant recipients without adenomatoid tumor (AT).

Age at operation (y)	Age at dialysis (y)	Age at transplant (y)	Obstetrical status	Medicines	Presenting symptom	Primary renal condition	Preoperative diagnosis
46	25	25	Parturition 1	PSL Cys	Hypermenorrhea	Unknown	Myoma
51	43	43	Nulligravida	PSL Cys MMF	No symptoms	IgA nephropathy	Cervical cancer
60	55	57	Parturition 2	PSL Cys MMF	Irregular menses	Nephrosclerosis	Endometrial cancer
42	36	37	Nulligravida	PSL TAC MMF	Irregular menses	Thrombotic thrombocytopenic purpura	Hematometra

PSL, prednisolone; Cys, cyclosporine; MMF, mycophenolate mofetil; TAC, tacrolimus.

actually only one patient who had undergone temporary peritoneal dialysis.

A patient who receives hemodialysis is in a state of chronic inflammation (Jofré et al., 2006). AT is frequently found with inflammation via pathological diagnosis. Some authors have reported that AT may have a posttraumatic or inflammatory origin; these investigators have proposed to stress the reactive, rather than the neoplastic, character of ATs (Nogales et al., 2002; Youngs and Taylor, 1967; Weiss and Tavassoli, 1988; Ross et al., 1989). The present study showed that the length of time on dialysis prior to renal transplantation is a risk factor for the development of adenomatoid tumors of the uterus.

There are approximately 300,000 end-stage renal disease patients who have received hemodialysis in Japan. Almost all patients receiving hemodialysis are waiting for a donor kidney. In our hospital, as a whole, 20% of cases, and 40% of recent cases, are performed as preemptive transplantation, which is a high level in Japan. None of the preemptive renal transplantation cases have supported the hypothesis that the length of time on dialysis before transplantation causes an increase in the incidence of AT.

There is a possibility that AT is a drug-induced disease caused by immunosuppressants. A recent report related AT to the immunosuppressed state in a patient with human immunodeficiency virus (Phitayakorn et al., 2011). Livingston et al. suggested that the extensive growth pattern of AT involving the entire myometrium, as well as its association with a component resembling multicystic mesothelioma, might reflect the patient's diminished ability to limit neoplastic processes (Bülent Tiras et al., 2000). It could be that the immunosuppressed state might promote AT rather than the immunosuppressive drugs themselves.

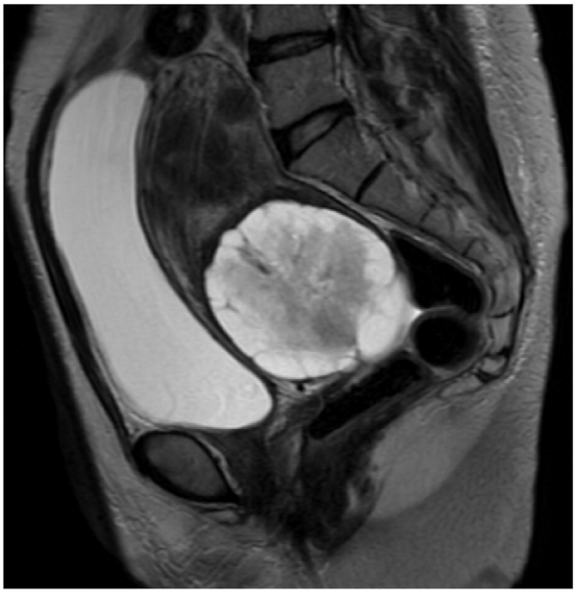

Fig. 3. Magnetic resonance imaging (MRI) scan of cystic adenomatoid tumor. The T2-weighted image revealed a 10.0-cm cystic tumor on the posterior wall of the uterus showing high signal intensity.

There are several limitations in this study. First, this study is retrospective design in single-centre site. Second, the number of admitted patients with renal transplant recipient was small. Additionally, renal transplanted patients have a better follow-up than other patients, leading may be to higher hysterectomy rate and better data collection in this group.

The present study showed that renal transplantation with immunosuppression therapy and length of time on dialysis are risk factors for the development of adenomatoid tumors of the uterus. Further studies are needed to explore these possibilities.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Role of the funding source

No funding sources were involved in this investigation.

Source of funding

There is no source of funding. These findings of this paper were not presented at a meeting.

References

Bülent Tiras, M., Noyan, V., Süer, O., Bali, M., Edali, N., Yildirim, M., 2000. Adenomatoid tumor of the uterus in a patient with chronic renal failure. Eur. J. Obstet. Gynecol. Reprod. Biol. 92, 205–207.
Cheng, C.L., Wee, A., 2003. Diffuse uterine adenomatoid tumor in an immunosuppressed renal transplant recipient. Int. J. Gynecol. Pathol. 22, 198–201.
Craig, J.R., Hart, W.R., 1979. Extragenital adenomatoid tumor. Evidence for the mesothelial theory of origin. Cancer 43, 1678–1681.
De Rosa, G., Boscaino, A., Terracciano, L.M., Giordano, G., 1992. Giant adenomatoid tumors of the uterus. Int. J. Gynecol. Pathol. 11, 156–160.
Ferenczy, A., Fenoglio, J., Richart, R.M., 1972. Observations on benign mesothelioma of the genital tract (adenomatoid tumor). A comparative ultrastructural study. Cancer 30, 244–260.
Golden, A., Ash, J.E., 1945. Adenomatoid tumors of the genital tract. Am. J. Pathol. 21, 63–79.
Jofré, R., Rodriguez-Benitez, P., López-Gómez, J.M., Pérez-Garcia, R., 2006. Inflammatory syndrome in patients on hemodialysis. J. Am. Soc. Nephrol. 17, S274–S280.
JSDT (The Japanese Society for Dialysis Therapy) (Ed.), 2009. Guideline for Peritoneal Dialysis.
Nogales, F.F., Isaac, M.A., Hardisson, D., et al., 2002. Adenomatoid tumors of the uterus: an analysis of 60 cases. Int. J. Gynecol. Pathol. 21, 34–40.
Phitayakorn, R., Maclennan, G., Sadow, P., Wilhelm, S., 2011. Adrenal adenomatoid tumor in a patient with human immunodeficiency virus. Rare Tumors 3, e21.
Ross, M.J., Welch, W.R., Scully, R.E., 1989. Multilocular peritoneal inclusion cysts (so-called cysts mesotheliomas). Cancer 64, 1336–1346.
Taxy, J.B., Battifora, H., Oyasu, R., 1974. Adenomatoid tumors: a light microscopic, histochemical, and ultrastructural study. Cancer 34, 306–316.
Tiltman, A.J., 1980. Adenomatoid tumors of the uterus. Histopathology 4, 437–443.
Weiss, S.W., Tavassoli, F.A., 1988. Multicystic mesothelioma. An analysis of pathologic findings and biologic behavior in 37 cases. Am. J. Surg. Pathol. 12, 737–746.
Youngs, L.A., Taylor, H.B., 1967. Adenomatoid tumors of the uterus and fallopian tube. Am. J. Clin. Pathol. 48, 537–545.