



Title	Fibroadenoma in adolescent females after living donor liver transplantation
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1 Introduction

2 Fibroadenoma of the breast (FA) is the most common solid lesion found in young women.

3 FAs usually form during menarche and are most commonly found in women aged 15 to

4 25 (1). There are no clear-cut data on the incidence of FA in the general population. In

5 one study, the rate of occurrence of FA in women who were examined in breast clinics

6 was 7% to 13% (2), while it was 9% in another study of autopsies (3). It is a benign

7 hormone-dependent neoplasm, which contains more estrogen receptors than the

8 mammary lobule (4). They are usually benign, with a documented malignant

9 transformation rate of less than 0.3% (5). Phyllodes tumors are closely related to FAs.

10 However, they may be locally destructive and have the potential to become malignant (1).

11 Since phyllodes tumors present in a similar fashion and share histological characteristics

12 with FA, surgeons may feel compelled to rule out phyllodes tumor with a core needle

13 biopsy because intervention would require wider excisional margins.

14 Female patients treated with cyclosporine have an increased risk of developing FA after

15 renal transplantation. Some patients require surgical management (4, 6-9). In these

16 previous reports, the incidence of FA has been reported to range from 11% to 39% in

17 female renal transplant patients receiving cyclosporine. However, FA after living donor

18 liver transplantation (LDLT) has not been described. Only one case report of *de novo*

19 phyllodes tumor after liver transplantation has been reported (10).

We have experienced a couple of adolescent female patients who had FA after LDLT. Therefore, we reviewed our LDLT patients in order to determine the incidence of FA and analyze the risk factors for FA in adolescent females after LDLT.

1. Patients and methods

1.1. Selection criteria

We retrospectively reviewed all patients in a maintained database who underwent LDLT between February 1998 and January 2015 at the Department of Pediatric Surgery, Osaka University Graduate School of Medicine. On September 1st, female patients aged 10 to 19 years who underwent LDLT and survived at least one year after transplantation were enrolled in our study. A total of 94 patients underwent LDLT at our hospital. Eighteen patients met the inclusion criteria and were enrolled in our study. To determine pre- or post-transplant conditions that are associated with FA after transplantation, the patients were divided into two groups according to the presence or absence of FA: FA group and non-FA group. FA was diagnosed histologically after physical examination. Ultrasound was used for diagnosis and negative screening. Age at LDLT, age at breast evaluation, indication for LDLT, immunosuppression regimen, and duration between transplantation and breast evaluation were analyzed retrospectively.

1.2. Immunosuppression

The immunosuppression regimen consisted of tacrolimus and low-dose steroids. The target whole blood tacrolimus trough level was 12–15 ng/ml during the first two weeks and 2–4 ng/ml thereafter. Methylprednisolone (1 mg/kg/day administered intravenously) was given on postoperative day 1, followed by 0.8 mg/kg/day on postoperative day 2, 0.6 mg/kg/day on postoperative day 3, and 0.4 mg/kg/day on postoperative days 4–6. Intravenous methylprednisolone was then switched to oral prednisolone (0.4 mg/kg/day) on postoperative day 7, and the dose was reduced to 0.1 mg/kg/day six weeks after LDLT. If the recipient had stable liver function, she was weaned off steroids at five months after LDLT. If the patient had side effects from tacrolimus, such as headache, confusion, convulsions, or uncontrolled rejection, she was switched to cyclosporine. The target whole blood cyclosporine trough level was approximately 100 mg/ml.

1.3. Investigation methods

A diagnostic ultrasound system made by the Hitachi Medical Corporation was used for all examinations (Hitachi model ProSound α7; Hitachi Medical Corporation, Tokyo, Japan). The breast glands were searched systematically for focal lesions using a radial scanning pattern. Lesions are considered FA if one of the following criteria was evident: well-circumscribed, round to ovoid or macrolobulated mass, generally uniform hypoechogenicity, and horizontal orientation.

The diagnosis of FA was made based on examination of core needle biopsies performed under ultrasonographic guidance. When there were multiple lesions, larger lesions were chosen for core needle biopsy. Histological analysis was performed with hematoxylin and eosin staining. Microscopically, FA develops at the expense of the terminal ductal lobular unit and contains a variable proportion of stroma and epithelial tissue. The stromal component is more or less cellular and may include myxoid and hyaline changes and calcifications (11).

2. Results

2.1. Demographic data

A total of 18 female patients aged 10–19 years who underwent LDLT at our hospital and survived for at least one year after transplantation were enrolled in this study. The demographic data of patients were described in Table 1.

2.2. FA cases and the incidence of FA after LDLT

Two of 18 patients developed symptomatic FA. Remaining 16 patients were found to have no FA by ultrasound examination. The FA lesion was multiple and bilateral in case 1, and solitary in case 2. Core needle biopsy of the masses under ultrasonographic guidance revealed that the histology was consistent with FA. Therefore, the incidence of FA after LDLT was 11.1% (2/18) in our patients.

Case 1 had an onset of autoimmune hepatitis at the age of 18 months, and she had been treated with azathioprine, methylprednisolone, and ursodeoxycholic acid. At the age of 14, she showed recurrent hematemesis from esophageal varices related to liver cirrhosis and received several sessions of endoscopic therapy for recurrent esophageal varices. Therefore, LDLT was indicated as a curative therapeutic option for end-stage liver disease caused by autoimmune hepatitis. She underwent LDLT from her father when the patient was 14 years old. The postoperative course was uneventful and the patient was discharged on postoperative day 39. The tacrolimus regimen was switched to cyclosporine-based 15 months after LDLT because of suspicious tacrolimus neurotoxicity. She noticed the mass in her right breast 18 months after LDLT. The mass enlarged with pain and reached 70 mm × 50 mm three months after she noticed (Fig. 1). She underwent surgical removal of the two masses in her right breast 21 months after LDLT. Pathological examination confirmed FA (Fig. 2). Because of the possibility that cyclosporine may induce the formation of FA, the regimen was switched to tacrolimus-based eight months after the start of cyclosporine therapy. The FA in her left breast which was noticed 19 months after LDLT started to decrease in size two weeks after the switch (Fig. 3). There were no adverse effects on liver graft function, and no complications were observed following conversion to tacrolimus.

Case 2 had undergone Kasai's operation for biliary atresia at 65 days old. Cyanosis and dyspnea had initially developed at the age of five years. The diagnosis of

hepatopulmonary syndrome was confirmed by contrast echocardiography and lung perfusion scan with ^{99m}Tc macroaggregate albumin. She underwent LDLT from her father for end-stage liver disease due to biliary atresia at five years old. The postoperative course was uneventful and the patient was discharged on postoperative day 82. The tacrolimus regimen was converted to cyclosporine-based 45 months after LDLT because of tacrolimus neurotoxicity that was proved by brain magnetic resonance imaging. She noticed the mass measuring 27mm in her left breast 89 months after LDLT. The patient refused conversion to tacrolimus, and her breast mass remained the same size, measuring 27 mm × 15 mm for 13 months.

2.3. Factors associated with FA after LDLT

In order to determine the risk factors for FA, the 18 patients were divided into two groups: FA group (n=2) and non-FA group (n=16). Demographic and clinical data of the patients by FA status are presented in Table 1. There were no differences in mean age at LDLT, mean age at breast evaluation, mean duration between transplantation and breast evaluation, and indication for LDLT between the two groups. However, there was a difference in the immunosuppressive regimen between the two groups. All 18 patients were initially on a tacrolimus-based immunosuppressive regimen. In two patients of FA group, the regimen was converted to cyclosporine-based because of tacrolimus neurotoxicity including headaches, confusion, and convulsions. The tacrolimus regimen

was switched to cyclosporine-based 15 months after LDLT in case 1 and 45 months after LDLT in case 2. In contrast to FA group, the tacrolimus-based regimen was maintained without any complications in non-FA group. There was a difference in immunosuppressive regimen between the two groups.

3. Discussion

Management of FA found in children and adolescents includes surgical resection or observation because complete tumor regression may occur in 10–59% of lesions (1, 12). Given the low rate of malignancy, guidelines for the management of pediatric breast lesions typically recommend a conservative approach (5, 13). Recommended indications for surgical excision include rapid growth, diameter greater than 5 cm, persistence without regression, systemic symptoms, personal history of malignancy or radiation, and concerning features on imaging (1, 13).

The relationship between FA and cyclosporine was first reported by Rolles and Calne in 1980 (6), who described two renal transplant recipients on cyclosporine who developed FA. One patient had had multiple bilateral lesions that resolved after withdrawal of cyclosporine. A prospective study reported by Iaria et al in 2010 (4) included eight patients who developed FA with cyclosporine-based immunosuppression after renal transplantation who were then converted to tacrolimus. Multiple FAs were observed in

seven patients, and six patients had bilateral lesions. Their study included 21 FAs in total. Among the 21 lesions, after conversion to tacrolimus eight disappeared and the majority of the remaining lesions decreased in size. In other previous reports, the incidence of *de novo* FA has been reported in the range of 11% to 39% in female renal transplant patients receiving cyclosporine (7, 9).

There are few reports of FA after thoracic organ transplantation when the posttransplantation maintenance immunosuppressive regimen included cyclosporine (14). The only case report of phyllodes tumor after liver transplantation involving a cyclosporine-based immunosuppressive regimen was reported by Cheng et al (10). However, there have been no reports of FA after liver transplantation. An association between FA and tacrolimus has not been reported.

In our sample of 18 adolescent female liver transplant recipients who survived more than one year after LDLT, the incidence of FA was 11.1%, which is similar to the previously reported incidence after renal transplantation. All patients in this study who developed FA were maintained on cyclosporine, and no patients maintained on tacrolimus developed FA. Furthermore, in the patient with FA who switched to tacrolimus, the tumor started to decrease in size two weeks after the switch. This phenomenon has been described in

female renal transplant recipients (4, 6). Our results indicate that the probability of developing FA appears to be determined by cyclosporine exposure following LDLT.

The mechanism of development of FA induced by cyclosporine is not understood. It has been suggested that cyclosporine may act directly on fibroblasts or have an effect on the hypothalamic-pituitary axis (15). Other researchers have suggested antagonism of prolactin receptor sites on B and T lymphocytes by cyclosporine (16). Although cyclosporine increases the risk of FA after renal transplantation, upon discontinuation of cyclosporine and switching to tacrolimus, regression of FA is possible (4). In our experience, cyclosporine may have a role of development of FA in LDLT patient as well as renal transplant patient.

Therefore, we recommend early evaluation involving breast ultrasound in adolescent women with symptoms of breast lumps on cyclosporine treatment after LDLT. Among women with FA, conversion to tacrolimus may reduce the size of FA.

In conclusion, cyclosporine is implicated in the development of FA in adolescent females after LDLT. In addition, our study suggests that the switch from cyclosporine to tacrolimus can effectively prevent the progression of FA.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by *Pediatric Transplantation*.

References

- 1) Sosin M, Pulcrano M1, Feldman ED, et al. Giant juvenile fibroadenoma: a systematic review with diagnostic and treatment recommendations. *Gland Surg*. 2015; 4: 312-321.
- 2) Greenberg R, Skornick Y, Kaplan O. Management of breast fibroadenomas. *J Gen Intern Med* 1998; 13: 640-645.
- 3) Franyz VK, Pickern JW, Melcher GW, et al. Incidence of chronic cystic disease in so-called normal breast: a study based on 225 post mortem examinations. *Cancer*. 1951; 4: 762–767.
- 4) Iaria G, Pisani F, De Luca L, et al. Prospective study of switch from cyclosporine to tacrolimus for fibroadenomas of the breast in kidney transplantation. *Transplant Proc* 2010; 42: 1169-1170.
- 5) Sklair-Levy M, Sella T, Alweiss T, et al. Incidence and management of complex fibroadenomas. *AJR Am J Roentgenol* 2008; 190: 214-218.

- 1 6) Rolles K, Calne RY. Two cases of benign lumps after treatment with cyclosporin A.
2 Lancet 1980; 11: 795
- 3 7) Seo YL, Choi CS, Yoon DY. Benign breast diseases associated with cyclosporine
4 therapy in renal transplant recipients. Transplant Proc 2005; 37: 4315-4319.
- 5 8) Hocke M, Selbach J, Dietrich CF. Cyclosporine-induced fibroadenomatosis. Ultraschall
6 Med. 2011; 32: 312-314.
- 7 9) Sangthawan P, Fox J, Atkins RC, et al. Increased incidence of benign breast disease
8 in female renal transplant patients receiving cyclosporin. ANZ J Surg. 2002; 72: 222-
9 225.
- 10 10) Cheng F, Qin JJ, Yu MN, et al. *De novo* phyllodes tumor in an adolescent female
11 after liver transplantation. Pediatr Transplant. 2011; 15: E12-14.
- 12 11) Kuijper A1, Mommers EC, van der Wall E, et al. Histopathology of fibroadenoma of
13 the breast. Am J Clin Pathol. 2001; 115: 736-742.
- 14 12) Jayasinghe Y, Simmons PS. Fibroadenomas in adolescence. Curr Opin Obstet
15 Gynecol. 2009; 21: 402-406.
- 16 13) Knell J, Koning JL, Grabowski JE. Analysis of surgically excised breast masses in 119
17 pediatric patients. Pediatr Surg Int 2016; 32: 93-96.
- 18 14) Zhang JW, Dry J, Moroz K. Pathologic quiz case: post-lung transplantation patient
19 with bilateral breast masses. Arch Pathol Lab Med. 2003; 127: 375-376.

- 1 15) Foxwell BM, Woerly G, Husi H, et al. Identification of several cyclosporine binding
2 proteins in lymphoid and non-lymphoid cells in vivo. *Biochim Biophys Acta*. 1992: 1138:
3 115-121.
- 4 16) Russell DH, Kibler R, Matrisian L, et al. Prolactin receptors on human T and B
5 lymphocytes: antagonism of prolactin binding by cyclosporine. *J Immunol*. 1985: 134:
6 3027-3031.