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CASE REPORT

Papillary Microcarcinoma of the Thyroid Gland in Renal Transplant Patients

Case reports and review of the literature

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Among organ transplant recipients there is a world wide increase in the number of de novo tumors as well as a decrease in the time of the first appearance after the transplantation. Between 1973 and the 31th of August 1999 1709 cadaver renal allograft transplantations were perfomed in our Department. Four thyroid cancers were detected among the renal transplanted patients. Two of them proved to be papillary microcarcinomas. Although the elevated risk of thyroid cancers is well established in the literature papillary microcarcinomas have never been reported before in an immunosuppressed patient. Authors highlight that the thyroid gland should always be carefully checked in organ transplant recipients, since better survival might be achieve even in the immunosuppressed population. Metastatic tumor is relatively benign which is in correlation with the literature, but there has been little experience in organ transplanted patients so far. (Pathology Oncology Research Vol 6, No 1, 72–75, 2000)

Keywords: papillary microcarcinoma, thyroid cancer, immunosuppression, renal transplantation

Introduction

The incidence of all thyroid cancers is estimated to be 0.05% in the general population.[14] Thyroid cancer accounts for about 1% of all neoplastic diseases,[7,8] with the incidence slowly increasing in most of the countries. In Hungary the morbidity rate is 1.8/100.000 inhabitants.[6]

With early diagnosis and active follow up strategy the mortality generally exhibits a falling tendency.[8] In Hungary there has been a slight increase during the last 30 years.[6] Malignant tumors frequently (4 to 18% of all patients) develop in organ transplant recipients.[15] Among the 1709 renal allograft recipients transplanted in Budapest (Hungary) between 1973 and 1999 we found 59 tumorous cases including 4 thyroid carcinoma (2 of them occult sclerosing microcarcinomas, and 2 ot them ordinary type). This frequency (4/1709) is higher than in the general non-immunosuppressed Hungarian population. The occurrence of sclerosing papillary cancer is a rarity in this population. All thyroid cancer cases occurred at least 8 years after the Chernobyl explosion, none of them before.

Case reports

Patient I. – a 54 years old female patient was transplanted because of chronic pyelonephritis in December 1992. Immunosuppression meant cyclosporin+steroid. As the only complication Herpes simplex infection was detected 7 days after the transplantation. Cholecystectomy was performed 18 months after the transplantation due to cholelithiasis. 19 months after the cadaver kidney was transplanted we diagnosed suspect nodules in the thyroid gland. Bilateral subtotal resection was performed. The histological report diagnosed a small, non-encapsulated sclerosing *papillary microcarcinoma (diameter = 0.8 mm)* in a multinodular goiter. The immunosuppression therapy was

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maintained. No signs of graft function damage were found. Seven years after the renal transplantation the patient is in good condition, with an excellent graft function. Check-ups for possible tumor propagation – including chest X-ray, bone scintigraphy, neck ultrasonography, and scintigraphy, thyreoglobulin test -have been found to be negative.

Patient II. – a 47 years old female patient was transplanted because of polycystic kidney disease in 1993. Immunosuppression meant cyclosporin+steroid. There was no complications for 3 years. In 1996 she was checked for viral (CMV) infection because of fever. The chest X-ray showed multiplex bilateral lung metastases. Gastroscopy, coloscopy, abdominal CT scan, and gynaecology didn't verify any primary locus. Percutan biopsy was taken from the pulmonal alteration. Histology verified metastatic carcinoma suspected to be of the papillary subtype. Collar ultrasonography and isotope scanning were performed, which verified goitre in the left thyroid lobe without isotope activity. Attempts to obtain histology result by biopsy remained unsuccessful three times. Immunosuppression was reduced to half dosage. Her own polycystic kidneys were investigated with CT, and ultrasonography. Percutaneous biopsy was taken from tumor suspect foci. All investigations were negative. Since no other loci were found thyroid cancer was suspected to be the primary tumor. Because of accidental left radius fracture, the operation was temporarily cancelled: bilateral total resection of the thyroid gland and the block dissection of the regional lymph nodes was performed. Pathology verified a ***well encapsulated sclerosing papillary microcarcinoma (10 mm in diameter),*** with psammoma bodies. The regional lymph nodes were not affected. Steroid was withdrawn and cyclosporin was given in half dosage. I^{131} treatment was first introduced then later rejected, due to the lack of iodine uptake of the tumor, proved by isotop scanning, and the pulmonal metastases. The number, size, and morphology of pulmonal metastases did not change in 1 year, but brain metastases occurred 1 1/2 year later, and the patient died 2 years after the transplantation.

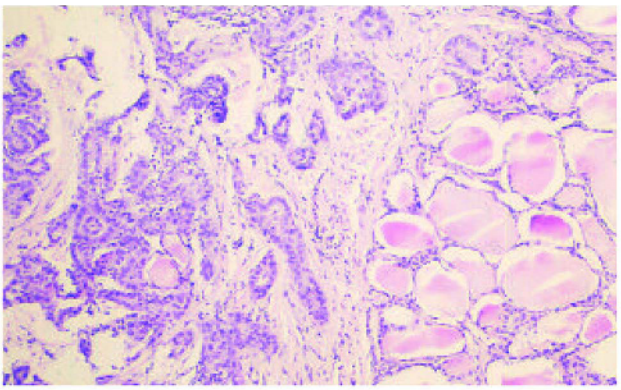

Figure 1. *Multinodular goiter. The follicles contain a large amount of colloid. Papillary neoplasm showing irregular border can be seen in the periphery, embedded into the collagen rich, hyalinized tissue. (Light microscopy, HE staining, magnification: 200 x)*

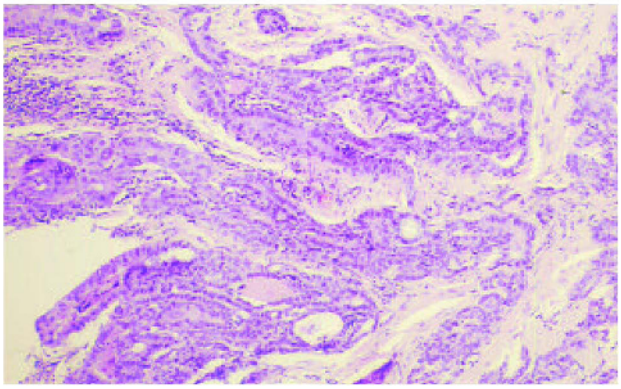

Figure 2. *Columnar, basophilic tumor cells, with signs of mitotic activity. Psammoma bodies are present at places. (Light microscopy, HE staining, magnification: 400 x)*

Patient III. – a 62 years old female was transplanted in 1993. Thyroid cancer was detected 14 months later. Bilateral nearly total thyreoidectomy was performed. ***(histology: papillary cancer – tumor diameter = 1.4 cm)*** . Regular check ups have not verified any recurrences or metastases.

Patient IV – was the only male (43 years old). He was transplanted in 1988. Steroid bolus therapy was introduced due to acute rejection, then gradually deteriorating graft function was verified. Angiography showed incipient chronic rejection. Triple therapy (cyclosporin+ steroid+azathioprin) was introduced. Thyroid cancer was detected in 1995, 84 months after the transplantation. Bilateral subtotal thyreodiectomy was performed, showing ***papillary cancer*** of the thyroid histologically ***(diameter = 1.5 cm).*** Four years after the operation the patient is still tumor-free and in good condition. Three patients of the four are still alive.

Discussion

Papillary cancer is the most common form of thyroid malignancy. Two major criterias are used for the recognition of papillary type carcinoma: the presence of true papillary formation and the cytologic features like ground-glass nuclei. The most common prognostic factors of morphology are as follows: tumor size (diameter), capsulation, margins (pushing or infiltrating), sclerohyaline or desmoplastic fibrosis, cystic changes, the presence of solid areas, multicentricity, blood vessel invasion as well as extrathyroid invasion.[4] Usually in 13-19 % of all papillary cases the tumor size was found to be less then 1 mm in diameter. Although several names have been used in the literature to describe this entity, the WHO prefers and suggests the term ***papillary microcarcinoma.***[10] ***Occult sclerosing microcarcinoma,*** is a morphologic variant of the papillary cancer.

Tumors were arbitrarily placed in this category when they mesured 1 cm or less in diameter and were accompanied by sclerohyaline and/or desmoplastic fibrous reaction.[4,9,12,21]

Pathology – This type of neoplasm is defined as a ***papillary microcarcinoma*** measuring 1.0 cm or less in diameter.[1,13,22] Grossly, in the multinodular goiter a very firm, greyish-yellow lesion is usually found. Histologically its central part contains dense, collagen-rich, partly hyalinized, radiating sclerosis with occasional calcified foci, and (in our case in the periphery) papillary neoplasm can be verify. (***Figure 1***) The predominantly columnar, slightly basophilic tumor cells exhibit round to oval, pale nuclei with scarce mitotic figures. Sometimes the nuclei expressly show opaque glass character and tiny, concentrically arranged psammoma bodies can be observed. (***Figure 2***) Usually (as in our case) there are no sign of angioinvasion, or hyperfunction. Three subtypes have been demonstrated by several authors.[4,9,1,21,22] encapsulated, non-encapsulated sclerosing, non-encapsulated non-sclerosing. They found that the papillary pattern become prominent if the tumor showed continuous growth. Some authors searched for the presence of intranuclear cytoplasmic inclusions, grooves, and colloid as microscopic evidence in aspirated cytology.[13]

Incidence/morbidity/prognosis – Papillary microcarcinoma is a fairly common finding in the adult population, irrespective of age and sex: meticulous histological investigations disclosed an incidence of 2.7-14.0%.[1,4,13,14,19] in consecutive autopsies or in routine thyroidectomy specimens. Certain reports found occult papillary carcinoma in up to 10-14 % of autopsy material from thyroid cancer cases.[19,22] Prognosis is generally found to be excellent: only 1 death and 4 lymph node metastases have been reported from a total of 107 cases during an average 7.5 year follow up by Engel et al.[5] There has been a report of a case with solitary pulmonal metastasis with a survival rate of 15 years by Sasaki et al.[18] Carcangiu et al found 6.4% of occult papillary microcarcinomas out of 241 thyroid cancers in general surgical material. They also found the prognosis quite excellent: 98 % of the patients were free of the disease.[4] According to other sources its prognosis is not quite as good as that of papillary carcinomas.[13,22] Morphology alone, however is not always of predictive value, because some cases can be exceptionally aggressive.[11] Although this is a fact one should keep in mind that even the smallest forms may metastasise to the cervical lymph nodes.[4,17] An adequate therapeutic approach is suggested to be lobectomy or thyroidectomy [4] plus levothyroxin treatment.[14]

General population – There is a world wide increase in the incidence of all type of thyroid cancers in the normal population.[7,8,19] The increased number of thyroid cancers

Table 1. **Gender and age matching among immunosuppressed and non-immunosuppressed (general) population in Hungary**

Years	*1994*		*1995*		*1996*		*1997*		*1998*	
	female	*male*	*female*	*male*	*female*	*male*	*female*	*male*	*female*	*male*
					Immunosuppressed population*					
No.	72	77	67	96	60	94	72	104	51	92
%	**48**	**52**	**41**	**59**	**39**	**61**	**41**	**59**	**35**	**65**
					F/M ratio: 41 vs 59 %					
					General population					
%	**52**	**48**	**52,1**	**47,9**	**52,2**	**47,8**	**52,2**	**47,8**	**52,2**	**47,8**
					F/M ratio: 52 vs 48 %					

Years		*1994–1998*		*1997*		*1997*	
Population		*Immunosuppressed*				*Non-immunosuppressed*	
		Cumulative		*Relevant year*			
Gender		*females %*	*males %*	*females %*	*males %*	*females %*	*males %*
Age group	0–10	**0,6**	*1*	**0**	*0*	**10,8**	*12,4*
	11–20	**7,1**	*6*	**13,8**	*3,8*	**12,8**	*14,63*
	21–30	**13,3**	*15,1*	**16,6**	*11,5*	**14,3**	*16,3*
	31–40	**16,7**	*17,7*	**11,1**	*18,2*	**11,9**	*13,2*
	41–50	**33,5**	*32*	**31,9**	*42,3*	**15,3**	*16,1*
	51–60	**22**	*20*	**23,6**	*18,2*	**12**	*11,41*
	61–70	**6,5**	*7,5*	**2,7**	*4,8*	**11,07**	*8,9*
	>71	**0**	*0,8*	**0**	*1*	**10**	*6,9*

*No of cadaver kidney transplantations

may be a consequence of the sophisticated diagnostic possibilities, the development in histology investigations, and there is a suspected role of Chernobyl explosion. A „pool" of individuals with *occult* thyroid cancers (in the vast majority of papillary type) is probably present in most population.[8] In our study all thyroid cancers were detected at least 8 years after the Chernobyl accident, with no case occurring before.

In renal transplant population papillary microcarcinoma has never been reported before, although the recipients exhibit a significantly elevated risk of all type of thyroid cancer. Considering the review of the 1709 renal transplanted patients of our Clinic *59 primary* malignancies, including *4 primary thyroid cancers* were detected so far. Although the EDTA-ERA registry found all type of thyroid cancer to be less frequent among renal transplant patient versus non-grafted ones,[2] our 4 cases represent a highly elevated incidence.

Satistical aspects – Table 1 shows the age and gender matches in the non-immunosuppressed versus immunosuppressed population for the last 5 years. Reviewing this datas we can state that the female/male ratio and the age matching is completely different in the immunosuppressed and general population. In addition 4 cases are few to calculate statistical analysis. The two gropus are then no comparable statistically.

Preexsisting malignancies among transplanted patients – According to the literature the recurrence rate of tumors is about 8-10 % among those suffering of cancer before transplantation. Penn found 39 preexsisting thyroid cancers (of 939 tumors) among 913 renal transplanted recipients,[16] and also a relatively low recurrence rate as contrasted with malignant melanomas or cancers of the urinary bladder.

Dialysed/non-transplanted population – Buccianti et al had performed a survey among patients on dialysis. 11 thyroid cancers (of any type) were found in 479 cancer cases. The elevation of incidence in primary thyroid cancer was statistically significant.[3] Early detection is important, because better survival can be achieved even in immunosuppressed patients. Nearly total or total thyreoidectomy, levo-thyroxin, and/or radioiodide treatment may be considered an adequate therapeutic approach for occult papillary cancer also in immunosuppressed patients.[20] The aim of this report is to call the attention to the regular check-up of the thyroid gland in renal transplant patients, because de novo carcinomas frequently develop in this population. All of above considerations are made with the realization that they are based on a retrospective study. A properly conducted prospective study would seem to be the best way of testing the validity of therapeutic suggestions including the role of immunosuppression. The good prognostic significance traditionally attached to the small primary tumors was confirmed in our population as well.

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