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CASE REPORT

Occult Thyroid Pathology in a Child with Acquired Immunodeficiency Syndrome

Case Report and Review of the Drug-related Pathology in Pediatric Acquired Immunodeficiency Syndrome

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A 11-year-old boy with acquired immunodeficiency syndrome (AaS), Varicella-zoster virus (VZV) infection and long-term antiviral treatment suffered from a disorder of contractility of the left ventricle of the heart. Following severe unmanageable vomiting, the patient died and the postmortem examination showed marked involution of the lymphatic system, multiple foci of fibrosis of both ventricles of the heart, and regressive changes of the thyroid gland. Biochemical values of the thyroid gland function were, however, not altered. Neither human immunodeficiency virus-related p24 antigen, nor VZV DNA sequences were found in the thyroid gland. Regressive changes of the thyroid gland can probably occur before its function fails. By analyzing the possible etiologies, the endocrine toxicity of a long-term antiviral treatment should be taken into account. (Pathology Oncology Research Vol 6, No 3, 227–232)

Keywords: HIV, AaS, childhood, thyroid gland, pathology

Introduction

Infection with the human immunodeficiency vírus (HIV) can induce a profound immunodeficiency which manifests itself in a broad spectrum of clinical and pathological features.[15,26] On pathological examination, the terminal HIV-infected patient usually shows severe depletion of lymphoid tissue and bacterial and opportunistic infections. Clinically, several alterations of the glucid, lipid and protein metabolism can be observed. The extent and magnitude of the dysregulation of the endocrine function may correlate with disease progression, but conflicting data regarding the thyroid function in children infected with HIV are present in the literature.[11] It is actually known that thyroid abnormalities occur more frequently than it was previously reported. HIV-ínfected children show frequently elevations of thyrotropin, total T4, total T3, and thyroxin binding globulin (TBG) concentrations in conjunction with low levels of free T4.[12]

In this report we describe a unique HIV-infected patient with regressive changes of the thyroid gland with reduction of the glandular parenchyma and pronounced fibrosis preceding a glandular dysfunction.

Case Report

The patient was a 11-year-old boy born with a perinatal HIV infection. The child was under the control of the Department of Pediatrics, University of Heidelberg, since the age of 4 years. B and T cell subpopulations as well as anti-retroviral treatment are shown in *Table 1*. A chronic varicella-zoster vírus (VZV) infection had been diagnosed and treated with aciclovir intravenously. *Pneumocystis carinii* prophylaxis had been performed with Cotrimoxazole. A chronic neutropenia had been treated with G-CSF. No cardiac or thyroid abnormalities, including

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Table 1. **B and T Cell Subpopulations in Blood (FACScan, Beckton Dickinson)**

Date	*WBC*	*Lym*	*CD 3*	*CD 19*	*CD 4*	*CD 8*	*CD 3- / CD 16+CD 56+**	*Antiviral Therapy*
Birth-1990	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1990	4.9	28	58	13	6	48	n.a.	n.a.
1991	2.4	49	62	18	15	41	n.a.	AZT
1992	2.1	43	50	2	14	34	n.a.	AZT
1993	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
1994	2.2	31	16	36	1	12	24	AZT
1995	1.4	40	23	27	1	21	15	AZT
1996	4.35	58	75	14	2	73	7	GCSF, SAQ, 3TC
Normal values (children, 7–17 years)								
Median	6.0	40	70	16	37	30	12	
P25-P75	4.7-7.3	36-43	66-76	12-22	33-41	27-35	9.0-16	

Abbreviations: * Absolute counts of WBC are expressed in 1000 cells mm-3, data are expressed as median together with percentile values. WBC: white blood cells, CD3 (T cells); CD19 (B-cells), CD 4 (T4-Lymphocytes), CD 8 (T8-cytotoxic lymphocytes), NK cells were derived from CD3 - / CD 16+ CD56+ Source: Hannet I. et al., Immunology Today 13: 215-218, 1992 (10); AZT: azidothymidine or zidovudine; SAQ: sanquinovir (a protease inhibitor); GCSF: Granulocyte colony stimulating factor; 3TC: 2',3'-dideoxy-3'-thiecytidine or lamivudine (an inhibitor of the viral reverse transcriptase); n.a.: not available.

thyroid hormones and anti-thyroid antibodies had been revealed on clinical and laboratory examination. In the last three months, the child developed a disorder of contractility of the lelt ventricle of the heart that was controlled with methyldigoxin. Digoxinaemia was in the normal range. Subsequently, he developed feeding intolerance and a severe unmanageable vomiting. Despite medical support, metabolic decompensation occurred and the child expired. Permission for a complete autopsy was granted by foster parents.

At postmortem examination, a hypotrophic child was seen (weight: 25 kg, height: 130 cm) with a marked involution of the lymphatic system. The thymus showed prominent depletion of lymphocytes, disappearance of the corticomedullary differentiation, hyalinization of the cortex, and micro- and macrocystic dilatation of the Hassal's corpuscles. Arterial hyalinosis and atrophic changes were seen in the spleen. No bacterial or fungal colonies were identified. There was cardiomegaly with dilatation of all chambers. Both ventricles showed moderate hypertrophy with increased size of muscle fibers on histologic examination. The anterior and posterior walls of both ventricles were mottled by small, but numerous foci of fibrosis. No evident necrotic myocytes were, however, discernible. The valves were unconspicuous and no foci of inflammatory infiltrate were seen. Intraalveolar fibrinous edema with very few plasmacells in the alveoli were also found in both lungs. Neither neutrophilic infiltrates, nor opportunistic microorganisms were detected. In the liver, a few lyrnphoid infiltrates were seen in the porfal triads. The brain showed cortical atrophy with bilateral inflammatory foci of monocytes in the medulla oblongata.

Grossly, the thyroid gland had a complete, intact, translucent capsule that allowed its separation from adjacent cervical structures. The consistency was rubbery. At the microscopic level a variety of morphologic changes were noted within the thyroid parenchyma. The thyroid gland showed extensive regressive change (*Figs 1a-d*). There were areas of the thyroid gland that showed pronounced fibrosis. In some fields dense and largely acellular collagen fibers divided the thyroid into small nodules. There were also some fields with free extraluminal colloid in the interstitial thyroid parenchyma. However granuloma formation or foreign body giant cells were not found. Intraluminal colloid ranged from pale staining with scalloped borders in some follicles (active secretory function), to densely eosinophilic staining (inactive secretory function). Rare areas also showed intraluminal colloid that tended to be broken up into globular formations. The follicular epithelium varied in shape from almost flattened to low columnar. An adipose metaplasia of the interfollicular stroma was also observed. C-cells were not increased.

At the time of autopsy, aliquots of heart and thymus tissue were snap-frozen and stored at 70°C until use. We performed an immunohistochemical analysis of the p24 antigen of human immunodeficiency virus (HN) (Dako Corporation, Hamburg, Germany) on paraffin-embedded sections of thyroid gland. No p24 antigen was detected. Further, we evaluated the antigenic expression of common leucocyte antigen (UCHL-1, mostly T cells), CD 20 (L26, mostly B-cell marker), CD 3 (all T cells), CD 4 (mostly helper/inducer T cells), CD 8 (mostly suppressor/cytotoxic T cells), and CD 68 (marker for monocytes and macrophages) (Dako Corporation) in heart and thymus tis-

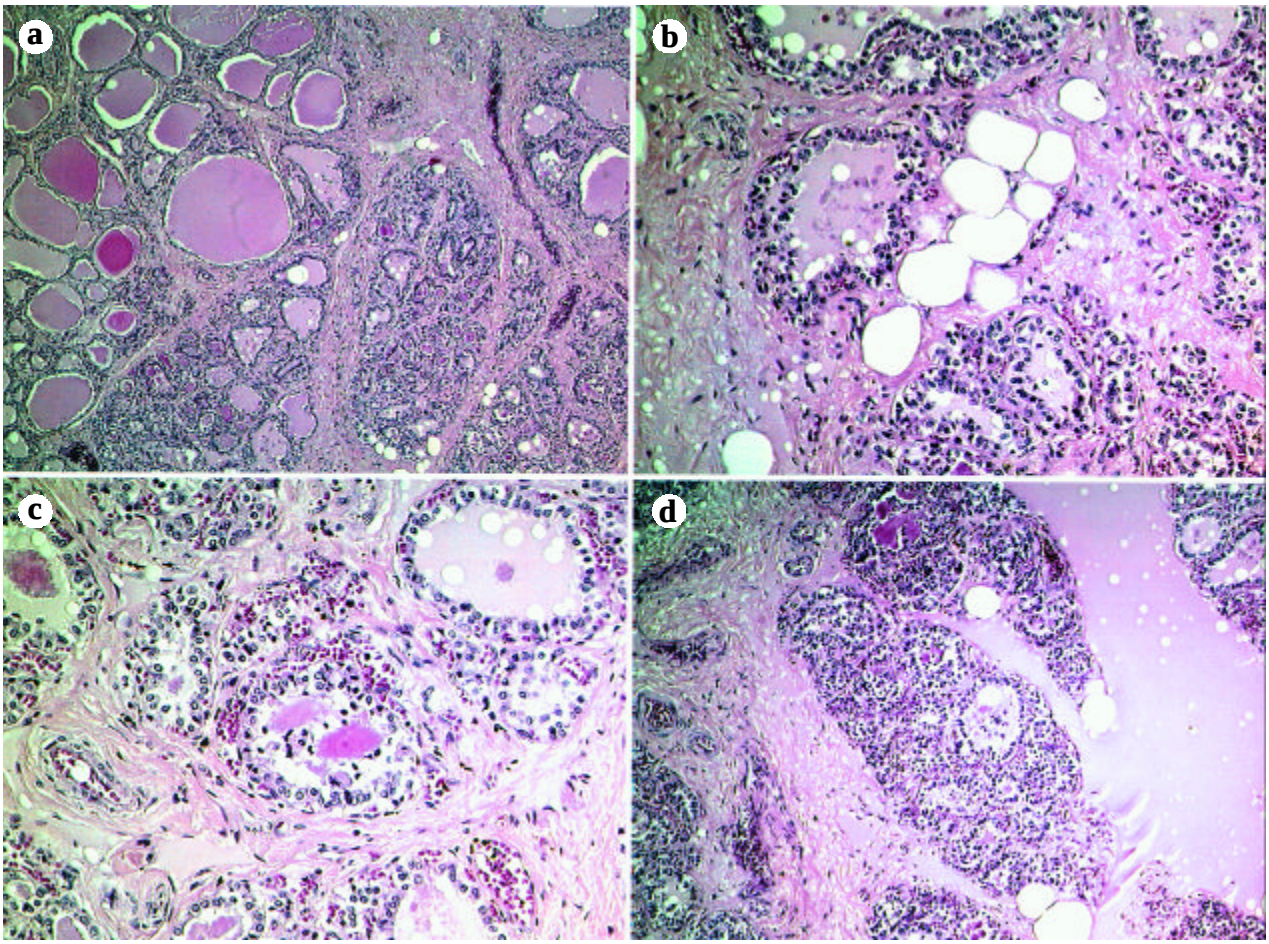

Figure 1. Thyroid gland showing pronounced fibrosis with inactive and active areas. Some follicles are increased in size, have a flattened epithelium, and have densely eosinophilic intraluminal colloid, whereas some follicles are normai sízed, lined by a single layer of columnar follicular cells, and have pale intraluminal colloid with scalloped borders (a, x50, hematoxylin and eosin stain). In some areas fibrotic septa contain collections of lipocytes (b, x160, hematoxylin and eosin stain), intraluminal colloid tends to be broken up in globular formations (c, x200, hematoxylin and eosin stain), or intraluminal colloid is free in the fibrovascular septa (d, x100, hematoxylin and eosin staín).

sues. Endogenous avidin-binding activity in sections was blocked using the Avidin/Biotin Blocking Kit (Vector Lab., Burlingame, CA, U.S.A.). Immunoperoxidase staining was performed using the avidin-biotin-peroxidase complex method of Hsu et al[14] and according to the instructions of the Vector Elite ABC Kit (Vector Lab.). Appropriate positive and negatíve controls were performed in each case. The p24 antigen of the HIV vírus was detected in the Kupffer cells, but no hepatocytes showed any signal. Heart and thyroid gland sections showed no p24 expression. Thymus sections showed expression of common leucocyte antigen (UCHL-1, mostly T cells) and CD 3 (all T cells). The T lyrnphocytes expressed almost exclusively CD 8 (mostly suppressor/cytotoxic T cells). In contrast, CD 4 (mostly helper/inducer T cells) was detected only on very few cells. High numbers of monocytes and macrophages were detected by staining for CD68. Immunohistochemical analysis of heart sections showed a moderate expression of CD68, whereas neither common leucocyte antigen (UCHL-1, mostly T cells) nor CD 20 (L26, mostly B-cell marker) could be detected.

Detection of VZV DNA sequences was evaluated in fresh material of skin, heart, and tongue as well as in deparaffinized material of thyroid gland. We detected VZV DNA sequences by nested PCR.[24] The following primer pairs were used: ATG TCC GTA CAA CAT CAA CT (VZV-7) and CGA TTT TCC AAG AGA GAC GC (VZV-8) as outer primer set; AAG CCC ATG AAT CAC CCT C (VZV-10) and GTA TGA TAT CCC GGT CGA TC (VZV-11) as inner primer set. The primers were synthesized using an automated DNA synthesizer (Beckman Instruments, Palo Alto, CA). Precautions were taken to minimize the risk of contamination of DNA extracts and reagents. Positive and negative controls were used. The

100 µl-reaction mixture consisted of 2 mM MgCl2, 20 mM Tris-HCI, and 16 mM (NH4)ZS04 using 10x Taq buffer (AGS, Heidelberg, Germany), 200 µM of each deoxynucleotide triphosphate (dNTP), 2 mM of each primer (VZV-7,-8 and VZV-10,-11), 5 pl of each DNA template, 2 U of Taq polymerase (AGS). Thirty-five cycles of amplification were performed in an automated DNA thermal cycler (Perkin Elmer-Cetus). Temperatures of the outer and inner primer annealing were 50° and 52°C, respectively. Twenty µl of the PCR products was run on a 2% agarose gel stained with ethidium bromide and visualized under ultraviolet light. VZV DNA sequences were detected in skin and heart, while no VZV DNA sequences were found in the thyroid gland (*Figure 2*).

Discussion

The pathology of the thyroid gland in AIDS has only rarely been object of morphologic studies. Regarding the dysfunction of the thyroid gland in HIV infected children different functional data have been reported. Schwartz *et al.* found an euthyroid status in 14 HIV-infected pediatric patients, but four of whom demonstrated elevated baseline and peak TSH level in response to thyroid releasing hormone, suggesting a state of compensated hypothyroidism.[25] By evaluating growth pattern, bone age, IGF-I secretion, and thyroid function in 24 perinatally infected children, Matarazzo et al. found that asymptomatic or paucisymptomatic patients had impaired growth, bone age delay, and reduced IGF-I levels, but none had thyroid dysfunction, contrasting with 40% of occurrence of thyroid dysfunction in patients with advanced disease.[21] Hirschfeld et al. measured total and free thyroxin, triiodothyronine, reverse triiodothyronine, thyrotropin and thyroxin binding globulin in 167 children with HIV infection and could identify free thyroxin at or below the lower limit of normal levels in 18% of children, and an ínverse correlation between CD4+ cell count and thyrotropin.[12] In regions of high incidence of HIV infection, an increased incidence of thyroid abscesses associated with HIV infection may occur.[6] Opportunistic infections, such as Pneumocystis carinii and Cryptococcus neoformans, have also been reported by histologic examination of the thyroid gland.[8,17]

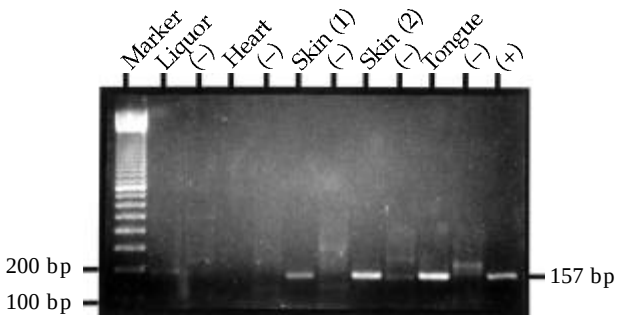

Figure 2. PCR detection of VZV. The amplified DNA from liquor, heart, skin (1 and 2) and tongue as indicated were separated on a 2% agarose gel. Heart and skin (1) were derived from our patient. The other tissue samples were obtained from different patients analysed on the same routine day. Upon visualization by ethidium bromide staining a VZV-specific band of 157 bp appeared in samples from skin (1 and 2) and tongue. A 100 base pair ladder (Pharmacia, Uppsala, Sweden) was used as a marker (lelt side). Each tube containing an amplified tissue sample was followed by a PCR reaction containing destilled water instead of extracted DNA as a negatíve control (-). As a positive control (+) DNA extracted from vesicle fluid harvested from a patient with varicella was used.

The pathogenesis of the fibrotic change in the thyroid gland remains to be elucidated. Presumably cellular hypoxia prevents cellular regeneration, resulting in scarring. A dysregulation of the hypothalamus-axis or toxic or allergic drug reactions may play a role in thyroid pathology by children with pediatric acquired immunodeficiency syndrome (PAIDS). It is known that fibrotic changes can occur in Riedel's thyroiditis, which is a rare form of chronic thyroiditis characterized pathologically by a fibrosing reaction that destroys more or less all the thyroid gland and simultaneously extending into surrounding neck structures. Although the histologic picture observed in our patient is different from that seen in the thyroid gland of patients with Riedel's thyroiditis, a hypothesis can be discussed. Likewise to the cardiac fibrosis without inflammatory infiltrates, the presence in our HIV-infected patient of fibrotic changes in thyroid gland might induce to prefer a systemic, probably, toxic or allergic drug reaction.

The therapeutic successes are realized frequently at the expense of an increase in adverse reactions to the drugs, which are summarily distinguished in (a) organ toxicity, (b) immunosuppression, and (c) onset of secondary neoplasms. The advantages of the therapy are normally greatly than the immediate and late risks of toxicity, and clinico-pathological knowledge of the lesions associated with specific drug protocols is useful to adjust the same therapy and set up new guidelines for treatment. With the approval of new antiretroviral agents, the classical picture of PAIDS is acquiring new aspects.[4,13,26] Pediatricians and pathologists must be aware of the presentations of adverse drug reactions in HIV infected children, a phenomenon, which has been called in another context the „Daedalus effect" of medicine.[2] Several antiretrovirally active substances that have been released for clinical use in adults are now applied also to HIV-infected children. All available drugs have 2 main targets, i.e., HIV-1 reverse transcriptase (RT) and HIV-1 protease. RT-inhibitors act via two different mechanisms: nucleoside analogues interrupt reverse transcription of HIV-RNA by chain termination of the resulting proviral DNA, while non-nucleosidic RT-inhibitors block the activity of the enzyme by steric inhi-

bition. It has been suggested that side effects (at least of the nucleoside analogue RT-inhibitors) may be explained by the concomitant inhibition of cellular DNA-polymerases, especially the mitochondrial DNA-polymerases γ and δ. Inhibition of mitochondrial DNA synthesis is thought to cause a distinguished pattern of drug-induced disturbances of organ function, which is typical for nucleoside analogue RT-inhibitors: bone-marrow failure, peripheral neuropathy, pancreatitis, myopathy and otherwise unexplained metabolic acidosis.[26] The action of inhibitors of the HIV-1 protease (PIs) seems to be very specific for their molecular targets. No known mammalian enzyme has been identified as a potential target for HIV-1 protease inhibitora up to now. Thus, the clinical and biochemical side effects related to the use of these drugs seem to be caused by direct gastrointestinal (including functional changes in liver and pancreas) and renal toxicity, and/or genetic differences in hepatic drug metabolism (cytochrome P450). However, recent studies on adults receiving highly active antiretroviral drug combinations reveal an increased incidence of disturbed glucose homeostasis and lipodystrophy after the prolonged use of Pis.[5]

Zidovudine (azidothymidine or AZT) was one of the first 2'-3'-dideoxynucleosides to cause inhibition of the reverse transcriptase of HIV. Since zidovudine readily crosses the blood-brain barrier, it is used for the treatment of neurological diseases associated with HIV infection. Early trials showed that zidovudine results in clinical and immunological improvements and prolonged life in patients with AIDS. However, hematological toxicity is the main drawback associated with zidovudine therapy, including granulocytopenia and anemia.[16] Headache, myositis and liver toxicity have also been reported as major organ toxicities. A reduction of drug toxicity was achieved by using the combination of zidovudine with other agents, such as aciclovir, or other 2';3'-dideoxynucleoside analogues.[16] Although HIV infection in children can be complicated by the development of cardiac disease, a decreased function of the lelt ventricle of the heart and changes in cardiac muscle mitochondria have been associated with the use of *zidovudine* in adults and in animal models, respectively. Also in the cohort of the Pediatric Branch of the National Cancer Institute, Bethesda, Maryland, U.S.A., AZT-related cardiomyopathy has been found.[7]

Didanosine (dideoxyinosine, ddI) alone is well tolerated during chronic administration, and toxicities are uncommon and usually reversible. In 41 % of patients, the CD4 count increased and was maintained at the higher level even after years of treatment.[22] In a multicenter, double-blind study, symptomatic HIV-infected children 3 months through 18 years of age were stratified according to age (<30 months or > or =30 months) and randomly assigned to receíve *zidovudine, didanosine,* or *zidovudine* plus *didanosine*.[9] In symptomatic HIV-infected children, *didanosine* alone or *zidovudine* plus *didanosine* were more effective than *zidovudine* alone. The efficacy of *didanosine* alone was similar to that of the combinadon therapy and was associated with less hematologic toxicity. Frequent toxicities of *didanosine* include diarrhea, abdominal pain, nausea and vomiting. A peripheral neuropathy, electrolytes abnormalities and hyperuricemia are reported as being unusual. Butler et al[3] found a pancreatitis in 7 of 95 children receiving *didanosine* and Levin et al[19] recently reported two cases of pancreatitis, one of which with rapid development of a pseudocyst. Domanski et al[7] found that the use of *didanosine* does not seem to increase the risk of cardiomyopathy. Liver abnormalities were found among 34 children with PAIDS treated with *didanosine* within 2–18 months after start of the drug administration.[18] Two children died of fulminant hepatic failure and four had a striking elevation of alkaline phosphatases. All of them receíved sulfa drugs and antifungal treatment, whereas three had a serology positive for hepatitis C vírus. Liver histology in the patients with fulminant hepatitis showed an extensive hepatic necrosis. Liver biopsy done in two other patients revealed a mild granulomatous hepatitis in one and nonspecific changes (i.e., steatosis and a mild inflammation) in the other. Other toxic effects of *didanosine* include peripheral neuropathy and retinopathy.[27] Multiple well-circumscribed depigmented lesions in the mid-peripheral retina characterized by loss of retinal pigment epithelium and partial loss of the choriocapillaris and neurosensory retina in areas of loss of retinal pigment epithelium are seen. Transmission electron microscopy showed numerous membranous lamellar inclusions and cytoplasmic bodies in the retinal pigment epithelial cells.[27]

Nevirapine, a nonnucleoside HIV-1 reverse transcriptase inhibitor, is rapidly absorbed, its clearance is more rapid in chronic dosing studies than predicted by single-dose studies and is more rapid in younger children than in adolescent children. Most frequent toxicities include skin rash, sedation, headache, diarrhea, nausea. Rarely, elevated liver enzyrnes and hepatitis may be seen.[20]

Zalcitabine (2';3'-dideoxycytidine or ddC) alone and in combinadon was studied in 15 children between 6 months and 13 years of age with symptomatic HN infection.[23] By using *zalcitabine* alone, no neutropenia or anemia is observed, but at a dosage of 0.04 mg/kg per day, skin rash and oral ulcers may develop. Administration of *zidovudine* with *zalcitabine* to children with prior *zidovudine* treatment did not result in a significant increase in toxicity compared with that resulting from *zidovudine* monotherapy and demonstrated improvement in immunologic and virologic surrogate markers.[1]

In this report, we described regressive change of the thyroid gland with marked reduction of the glandular parenchyma and pronounced fibrosis preceding a glandular dysfunction in a HIV- and VZV-infected child with long-term antivi-

ral treatment. Morphologic changes of this type would not compromise the function of the thyroid gland of many subjects. Dysfunction of the thyroid gland may be seen in children with HIV-infection at an advanced stage, but the alteration of the morphology of the glandular parenchyma may frequently precede the state of glandular dysfunction. Drug-related cardiotoxicity and thyroid toxicity may have common pathogenetic mechanisms that need to be evaluated.

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