

Interferon-induced progression of autoimmune thyroiditis with enlarged thyroid glands in gynecological patient: A case report and literature review

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ABSTRACT

A case report presents a progression of autoimmune thyroiditis with an abnormal enlargement of the thyroid glands and increased thyrotropin hormone concentration-associated with interferon treatment in human papillomavirus infected patient with the autoimmune thyroiditis and a daily L-thyroxin hormone replacement therapy background. Observation was supplemented with a brief review of literature and discussion. On the basis of this observation and a brief review of literature authors suggested that the potential adverse effects of interferon therapy are over-balanced than its benefits for gynecological patients, therefore any interferon treatment should be recommended with strict indications as well as after screening of conditions and functions of thyroid glands and other interferon target organs to avoid interferon treatment side effects. Practitioners especially gynecologists should inform their patients about pleiotropic interferon effects and its high frequent and wide range side effects before to start such kind of treatment.

Keywords: Autoimmune Thyroiditis; Human Papillomavirus; Interferon; Thyroid Glands

1. INTRODUCTION

Interferon (IFN) is widely used cytokine as an adjuvant treatment of malignant diseases such as melanoma [1], renal cell carcinoma [2,3], hairy cell leukemia [4], Kaposi's sarcoma [5]. It also has been extensively used to

treat hepatitis B and C [6,7], as antiviral therapeutic agent.

Wide range of IFN treatment (IFN-TRT) side effects, due to pleiotropic mechanisms of its action, were described, including neuropsychiatric and neurobehavioral complications [8,9], IFN-induced depression [10], sexual dysfunctions [11], plural disturbances [12] and thyroiditis [13-15].

Fentiman *et al.* described a primary hypothyroidism in three patients with breast cancer during a trial of adjuvant IFN- α -TRT [16]. Since IFN-induced thyroiditis (IIT) were recognized as one of common side effects of IFN-TRT. The incidence of IFN-induced thyroid autoimmunity according to Oppenheim *et al.* ranged from 2.5% to 42%, possibly depending upon dose and duration of IFN-TRT and patient characteristics [17], whereas the rate of IIT by Tomer and Menconi was reached up to 40% in patients with hepatitis B and C, including the rate of clinical manifestations of IIT up to 10% and subclinical autoimmune thyroiditis up to 30% [18].

IFNs have been also widely used to treat genital warts, although their benefits were not clear [19]. Recently Yang *et al.* systematically reviewed 12 randomized controlled trials involving 1445 patients and concluded that IFN tends to be a fairly well-tolerated when it was locally used than its systemic administration to treat patients with genital warts [20]. However side effects of IFN-TRT in gynecological patients were not described yet.

2. CASE DESCRIPTION

26-year-old patient with subtle layer acetowhite lesions around external ostium of cervix uteri had abnormal low

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grade Pap smear (CIN1). Repeat DNA human papilloma virus (HPV) tests presented a persisted high risk HPV infection (16 and 18 genotypes). Patient has been under a medical supervision of an endocrinologist since thyroid hypofunction and autoimmune thyroiditis (AIT) was diagnosed. A size of left thyroid gland lobule was 14.5 cm³ and right—15.1 cm³ by means of ultrasound examination. A thyrotropin hormone (TSH) concentration was 0.88 mIU/L (reference values—0.4 - 4.5 mIU/L). Patient had received a hormone replacement therapy with 75 mg daily L-thyroxin and her condition was stable without AIT progression.

At the appointment a gynecologist due to cervical lesions with an abnormal low grade Pap smear (CIN1) and repeat DNA HPV positive tests decided to treat cervical lesions with conservative medications and prescribed several courses of IFN-TRT by turn. The treatment has continued before and after cryodestruction of cervical lesions and prolonged for 8 months but HPV persistence remained unchanged.

Patient received two courses of rectal suppository with IFN- α 2 (500,000 IU) twice daily for 10 days and 15-intracervical injections of IFN- α 2 (3,000,000 IU) every-other-day. In the end of IFN-TRT, patient experienced weakness, rapid fatigability and other symptoms of AIT progression and a noticeable abnormal enlargement of the thyroid glands and she went back to the endocrinologist, who registered progression of AIT with abnormal enlargement of thyroid gland lobules: left till 24.3 cm³, and right—17.8 cm³ by ultrasound, with increased values of TSH—till 8.4 mIU/L (**Table 1**). In order to stop progression of AIT daily dose of L-thyroxin was increased till 150 mg. An IFN-TRT was immediately halted. After 7 months HPV infection spontaneously disappeared and after 1 year patient had a baby.

3. DISCUSSION

In our case, unfortunately the gynecologist was not aware about possibility of IFN-induced thyroiditis development, especially in this patient with thyroid hypofunction and

Table 1. Patient condition, size of thyroid glands, concentration of thyrotropin hormone (TSH) and daily dose of L-Tyroxine before and after interferon treatment (IFN-TRT)

Parameters	IFN-TRT		Outcome
	before	after	
Patient's condition with background hormonal replacement therapy	stable	relapse	relapse
Ultrasound size of the thyroid gland lobules, cm ³			
Left	14.5	24.3	up to 67.6%
Right	15.1	17.8	up to 27.0%
TSH, mIU/L (Reference values: 0.4 - 4.5)	0.88	8.4	up to 10 fold
Dose of L-Tyroxine, mg	75	150	up to 2 fold

AIT. Even, when patient complained on weakness, rapid fatigability and other symptoms of AIT progression and a noticeable abnormal enlargement of the thyroid glands treatment was prolonged. IFN-TRT was canceled when patient was consulted by endocrinologist and a noticeably enlargement of the thyroid glands was registered by ultrasound with increased values of TSH and there was necessity to substantially increase the daily dose of L-tyroxine treatment.

In general, the main reason of this case was commercialization and compartmentalization of medical services, aggressive marketing of pharmaceutical companies as well as lack of systemic postgraduate education of practitioners during last a quarter of a century in RF and CIS countries. More than 120 immune tropic agents were registered in RF, most of them without relevant results of randomized clinical trials. Consequently uncontrolled use of immune modulating drugs is a widespread events in a routine of physicians, even they did not know indications or contraindications of those medications [21]. Clinical guidelines concerning immune modulating medications were mostly written by engagement of pharmaceutical companies [22] and the meetings of professional societies are being an important platform to realize aggressive marketing campaigns of pharmaceutical industry as well as mass media is widely used to reach this purpose. Therefore, unfortunately physicians misinformed and this case was happened as a consequence of such paradoxical situation in healthcare systems of these countries.

The IFN-triggered dramatic enlargement of thyroid gland size and progression of its dysfunction in our patient was related with combination of two factors: a background AIT with thyroid hypofunction and the INF-TRT. This patient would not suffer this IFN side effect at all, if gynecologist was interested in a background condition of this patient and a possible dysfunction of IFN target organs before to prescribe IFN-TRT. In spite of short prolongation and lower dose of IFN-TRT in comparison with modes of cancer or hepatitis adjuvant IFN-TRT, background conditions of our patient with AIT and thyroid glands' hypofunction were contributing factors of IIT. These results correspond with findings according to review by Ward and Bing-You that in patients receiving IFN-TRT, identifiable risk factors for developing autoimmune thyroid dysfunction are preexisting overt thyroid or autoimmune disease, subclinical thyroid or autoimmune thyroid disease, and female gender [23].

IFN-induced destruction of thyroid cells and their function impairment were shown in thyroid cell culture and in vivo experiments. So, Caraccio, *et al.* in primary human thyrocyte cultures [24] demonstrated an inhibitory effect of both IFN- α/β on the TSH-stimulated gene expression of thyroid peroxidase (TPO), sodium/iodide

symporter (NIS), and thyroglobulin (Tg) as well as free thyroxin T(4) release and concluded that the development of hypothyroidism during IFN-TRT may be related, at least in part, to an abnormal expression and function of key proteins involved in iodine uptake and organification [24].

Later Caraccio *et al.* in primary thyrocyte cultures showed that both IFNs increase apoptosis, indicating a possible pathway of development and progression of IFN-TRT-associated thyroid disease [25]. Based on these direct IFN thyroid effects and well-known basic IFN-immune mediated effects Tomer and Menconi proposed a pathogenesis of IIT (**Figure 1**) as [18]: “IFN- α direct thyroid toxic effects include upregulation of thyroid-specific proteins, such as thyroid stimulating hormone receptor (TSHR) gene, Tg, TPO, NIS expression, as well as induction of heat shock proteins (Hsp) expression, and thyroid cell death, whereas IFN- α immune effects include activation of immune cells, switching the immune response to Th1 pathways or cellular immune response, down regulation of regulatory T (Treg) cells, and induction of cytokine release e.g. interleukin (IL-6), and increased major histocompatibility complex (MHC) I expression. IFN- α also increases activity of immunocompetent cells such as lymphocytes, macrophages, NK-cells, neutrophils and monocytes. The combination of direct thyroid toxicity and immune stimulation can cause the release of thyroid auto-antigens and their presentation to resident T-cells, initiating an autoimmune response by a bystander mechanism” [18].

Although mechanisms of autoimmune reaction in IFN-induced destruction of thyroid cells during IFN-TRT are not clear yet. Recently many researches have supported

hypothesis concerning the induction of thyroid autoimmunity by IFN-TRT.

Akeno *et al.* described a development of marked inflammatory thyroid destruction associated with immune cell infiltration of thyroid and surrounding tissues leading to profound hypothyroidism in transgenic mice [26]. Surprisingly, upregulation of pathways in transgenic mice thyroid glands was similar to those observed in cultured thyrocytes, which facilitated Akeno *et al.*, to conclude that taken together, these results demonstrate that the induction of tissue inflammation and autoimmunity by IFN- α involves direct tissue toxic effects as well as provocation of destructive bystander immune responses [26].

It was shown, that independently of new IFNs implementation with improved pharmacokinetic and pharmacodynamic properties such as pegylated IFN their adverse effects were not diminished [27].

Minami *et al.* systematically reviewed with metaanalysis of the rates of IFN-TRT-related deaths and serious adverse events among 27,569 patients and concluded that the mortality rate during IFN-TRT was acceptably low, but the rate of serious adverse events was not negligible in a treatment for a benign disease [28].

Recently, Tran *et al.* in their review, summarized the worldwide current management and follow-up guidelines for patients undergoing IFN-TRT and suggested monthly screening test with TSH level whilst receiving combined ribavirin and IFN- α -TRT [29]. In a case of abnormal TSH levels recommend to sequentially evaluate free thyroid hormone parameters.

Owing to wide range of IFN-TRT side effects and doubtful IFN-TRT benefits in patients with genital warts and HPV-associated lesions [19], we speculate that

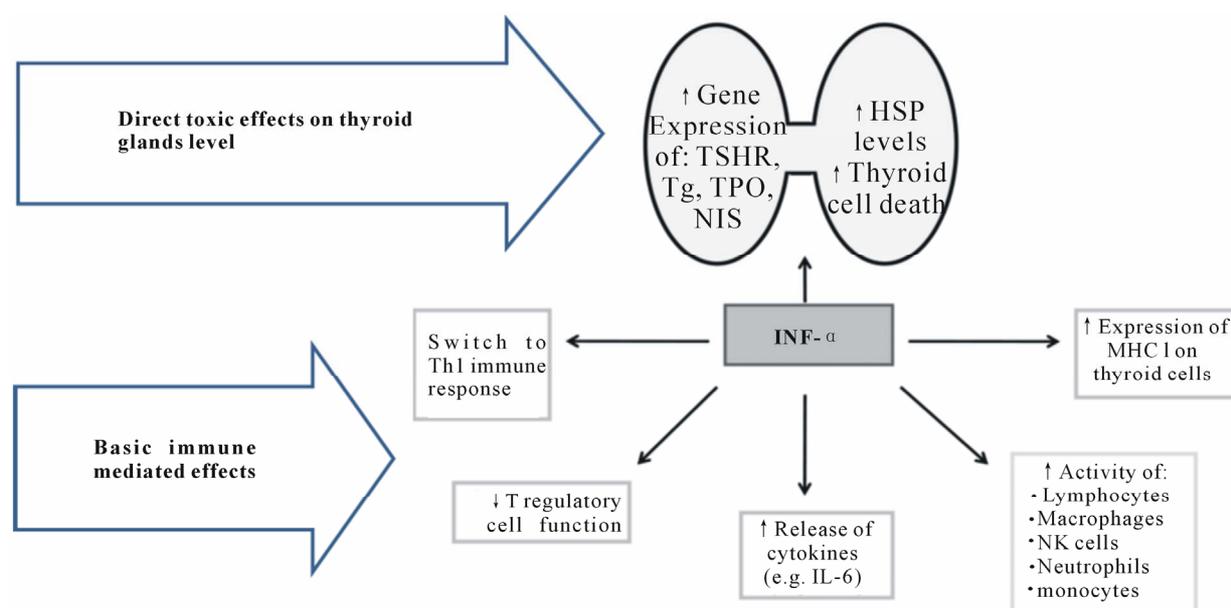


Figure 1. IFN-induced direct thyroid toxic and basic immune mediated effects. (Modified from Tomer and Menconi [18])

IFN-TRT in gynecological patients should be used only in cases of special needs with monitoring a function of IFN-target organs such as thyroid glands.

4. CONCLUSION

On the basis of this observation and a brief review of literature we suggest that the potential adverse effects of interferon therapy are overbalanced than its benefits for gynecological patients, therefore any interferon treatment should be recommended with strict indications as well as after screening of conditions and functions of thyroid glands and other interferon target organs to avoid interferon treatment side effects. Practitioners especially gynecologists should inform their patients about pleiotropic interferon effects and its high frequent and wide range side effects before to start such kind of treatment.

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