Mans. Med. J. *Vol. 51. Issue 4*, 2022, Pages 233-245

Mansoura Medical Journal

(Official Journal of Mansoura Faculty of Medicine)

pISSN: 1110-211X; **eISSN:** 2735-3990

Endocrinopathies as a price of cancer treatment

Jalila Abduljalil[1] , Hanan Abdl-hay[2]

1 Mansoura Manchester Medical student, Faculty of Medicine Mansoura university, Egypt

2 Lecturer of diabetes and endocrinology, Faculty of Medicine Mansoura university, Egypt

DOI: 10.21608/mjmu.2022.128620.1091

Submit Date: 25 March 2022
Accept Date: 17 October 2022
Available online: 01 Dec. 2022

Keywords

- Immunotherapy
- Endocrine
- cancer

Abstract

Many drugs are used in treatment of cancer. Including chemotherapy, hormonal therapy and immunotherapy. The investment of immunotherapy has improve the procedure for treating cancer by utilizing the immune system to identify and attack cancer cells through immune checkpoint inhibitors. This is done by two major mechanisms, the first is CTLA-4 inhibitors like ipilimumab, and the second pathways is PD-1/PD- L1 inhibitors like nivolumab. However many adverse effects have aroused as a consequence of immunotherapy usage. Including non-endocrinal adverse effects like colitis and dermatitis, and endocrinal side effects predominantly involving pituitary and thyroid gland plus the endocrine pancreas. Pituitary gland involvement is potentially life threatening and is mainly due to CTLA-4 inhibitors, leading to multiple pituitary hormone deficiencies. It mainly present with headache, and pituitary enlargement is reported in MRI. Which is treated by high dose glucocorticoids to prevent chiasmal compression. Hormone replacement therapy is required according to the deficient hormone. Thyroid gland is one of the most commonly involved glands. Predominately by a combination of both PD-1 and CTLA-4 inhibitors. It mainly present with transient hyperthyroidism followed by hypothyroidism, which is treated by levothyroxine replacement therapy. Immunotherapy will result in both endocrine and exocrine dysfunction. ICIs associated DM is classified into four different types according to the pathology. It includes all of Acute autoimmune insulin-dependent diabetes, type 2 diabetes-like phenotype, autoimmune pancreatitis-induced diabetes, and diabetes after autoimmune lipoatrophy. Patients presented with d ketoacidosis are treated with standard approach while stable patient will be subjected to a regular insulin regimen.

Corresponding author: Ahmed, Jalila , Mansoura Manchester Medical student, Faculty of Medicine Mansoura university, Egypt. Email: jalilaahmed@students.mans.edu.eg , Tel. 0097337732644

Introduction

Nowadays immunotherapy drugs are known for cancer treatment. It depends upon stimulating certain immune pathway that harass the tumor cells leading to its death. One of the types is immunotherapy with immune checkpoints inhibitors (ICIs) that has two different pathways to destroy cancer cells. The first relays on targeting the cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) pathway, like Ipilimumab. Other drugs like Nivolumab and Atezolizumab target the program death-1 receptor or ligand (PD-1 or PD-L1) route. [1] ICIs were first demonstrated in the treatment of malignant melanoma with Ipilimumab, and then the combination of Ipilimumab and Nivolumab was acknowledged as a first-line treatment that increased the survival of patients with metastatic cancer considerably.[2] However the use of immunotherapy has been associated with immune related adverse effect in multiple organs, including colitis, hepatitis and dermatitis, it is important to note that these effects are manageable with great suspected recovery.[3] Endocrinopathies were reported as an adverse effects for immunotherapy, mainly involving the thyroid and pituitary glands. As ICIs targets CTLA-4 and PD-1 pathways which are involved in the innate immunity of thyroid and diabetes diseases. The blockage of these routes lead to the evolution of endocrinal dysfunction that is similar to the natural autoimmune endocrine disease. [4]

This review aims to discuss the mechanism of immune checkpoint inhibitor mediated tumor cell death, and the resultant adverse effects in pituitary gland, thyroid gland and the endocrine part of the pancreas.

3. About immunotherapy

Immunotherapy is treatment that utilizes the immune system to attack diseases such as cancer. For example it enhances the natural defenses of immune system to attack cancerous cells. One of the types is Immunotherapy with ICIs that basically direct the immune system to recognize and attack the cancer cells, as it is describes in **figure (1).** [1]

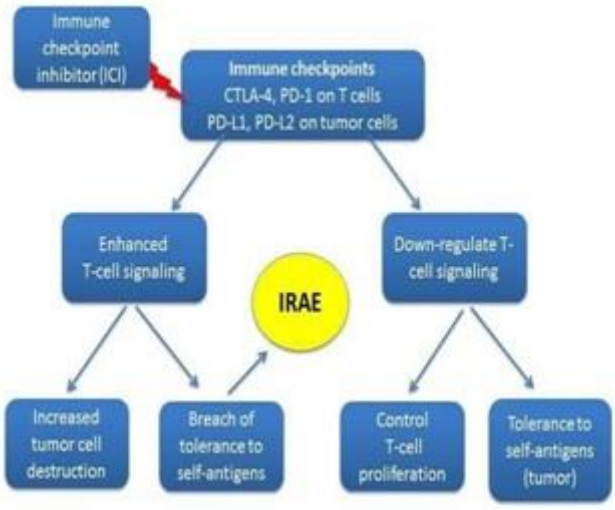

Figure (1): Mechanism of action of immune checkpoint inhibitor immunotherapy [1]

It has altered the cancer treatment by manipulating the immune system. T-cell activation is modulated by immunological mechanisms that are hindered by ICIs. The first, such like Ipilimumab, inhibits the cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) axis, whereas the other, such as Atezolizumab, Nivolumab, Durvalumab, and Pembrolizumab, inhibit the programmed death-1 receptor or ligand (PD-1 or PD-L1) axis. [5]

A T-cell receptor named CTLA-4 conflicts alongside CD28. (cluster of differentiation) for the antigen-presenting cell's co-stimulatory molecule B7. CTLA-4 does not create a stimulatory signal, thus limiting T-cell function by blocking the triggering CD28/B7 and T-cell receptor/major histocompatibility complex circuits. As it is shown in **figure (2).**

CTLA-4 inhibition promotes effector T cell activation and proliferation while suppressing immunosuppressive regulatory T cells. [5]

PD-1, which is a constituent of the CD28/B7 class is apparent on T cells. Interacting with PD-1 ligands impairs T-cell multiplication, immunostimulatory cytokine manufacturing and T-cell viability. The functional point of the immune system response is modified when PD-1 or PD-L1 is restricted, regaining T cell activity in the periphery. [1]

Immunotherapy has been associated with many side effects. For instance colitis and dermatitis were reported. Endocrine adverse effects of ICIs are amongst the more common immune related adverse effects (irAEs) described, predominantly pituitary and thyroid dysfunction, but diabetes mellitus has also been reported.[4] As it is shown in **table (1).** Disruption of the endocrine system is usually not reversible and require lifelong hormone replacement therapy. If not detected and treated early, endocrine disturbance can result in increased morbidity and mortality. As a result, practitioners should be alert to the signs and symptoms of ICI endocrine adverse reactions.[6]

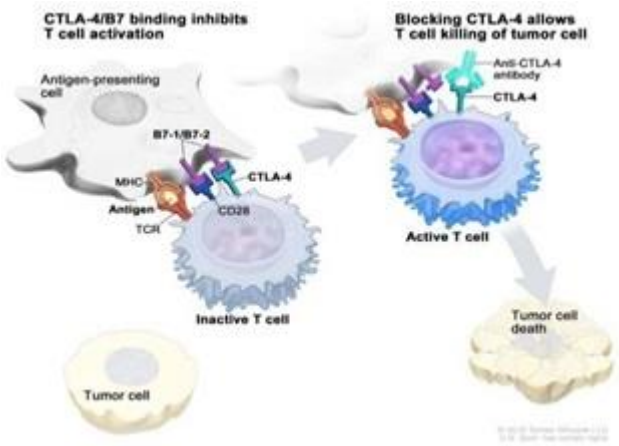

Figure (2): CTLA-4 mediated tumor cell death [5]

Table (1): Endocrine toxicities related to immune checkpoint inhibitor [4]

		CTLA-4 inhibitor	PD-1/ PD-L1 inhibitor
Pituitary	Hypophysitis/ hypopituitarism Isolated ACTH deficiency	+ + + +	- + +
Thyroid	Thyroiditis/transient hyperthyroidism Hypothyroidism Graves's disease/ thyroid eye disease	+ + + + +	+ + + + + + unknown
Pancreas	Insulin deficient diabetes	Not described	+ +
Adrenals	Primary adrenal insufficiency	+	+
+ + + >5% ***+ + 0.5-5%*** ***+ < 0.5%***			

4. Pituitary dysfunction associated with ICIs

Pituitary irAEs have existed as a significant and potentially life-threatening side effect. Two different pathways of pituitary involvement are shown in **figure (3).** Ipilimumab, a CTLA-4 inhibitor administered alone or in conjunction with a PD-1 inhibitor, induces a disease that mimics lymphocytic hypophysitis, with pituitary gland enlargement and various pituitary hormone deficits.[7] Pituitary gland affection is less typically linked to PD-1 and PD-L1 inhibitors. However, isolated adrenocorticotropic hormone (ACTH) insufficiency is the most frequent complication. [8] Pituitary irAEs has been reported following melanoma and kidney cancer patients were treated, with higher incidence in patients treated with a both ipilimumab and nivolumab; the risk of Pituitary irAEs is more in men and with older age. [9]

Figure (3): Different pathways of pituitary glands irAEs [7]

The mechanism of action of pituitary irAEs

The pathological mechanism of CTLA-4 inhibitor is known to be autoimmunity with lymphocytic destruction of pituitary gland, as its shown in **figure (4).** This is promoted by the fact that a combined regimen of ipilimumab and cytotoxic chemotherapy is not associated with hypophysitis, mainly due to lymphocyte depletion caused by the cytotoxic agents. Iplimumab is also eligible of inducing autoantibodies production.[10] Ipilimumab-induced hypophysitis (IH) affects the anterior pituitary by antibody induced mechanism, which predominantly recognize thyroid stimulating hormone (TSH) secreting cells and to less extent follicular stimulating hormone (FSH)- or adrenocorticotropic hormone

(ACTH) -secreting cells. It is now known that type II hypersensitivity reaction is the trigger for IH, in which the CTLA-4 antibody binds to the cognate antigen (prolactin and TSH- producing cells) expressed on pituitary cells, then it activates the complement, which initiates tissue destruction.[11] Lack of expression of CTLA-4 antigen could explain why posterior pituitary dysfunction in the form of diabetes insipidus is not common in IH. [12]

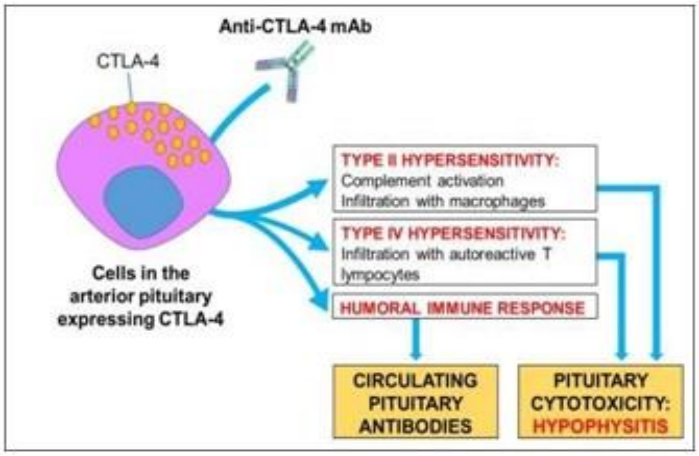

Figure (4): Mechanism of pituitary gland irAEs. [10]

Presentation of irAEs.

IH early occurrence has been described to be after first exposure to ipilimumab by four weeks, but the median time interval of IH is eleven weeks. [13] the most common presentation is headache. Other presenting symptoms are nonspecific and include weakness, fatigue, confusion, memory loss, hallucinations, labile mood, insomnia, temperature intolerance, chills, anorexia, decreased libido, and erectile dysfunction. Pituitary swelling has been associated with visual impairment [14]. Magnetic resonance imaging (MRI), is recommended, to assess pituitary enlargement, as its shown in **figure (5)**. Also to eliminate pituitary metastasis as an additional potential cause of hypopituitarism. [15]

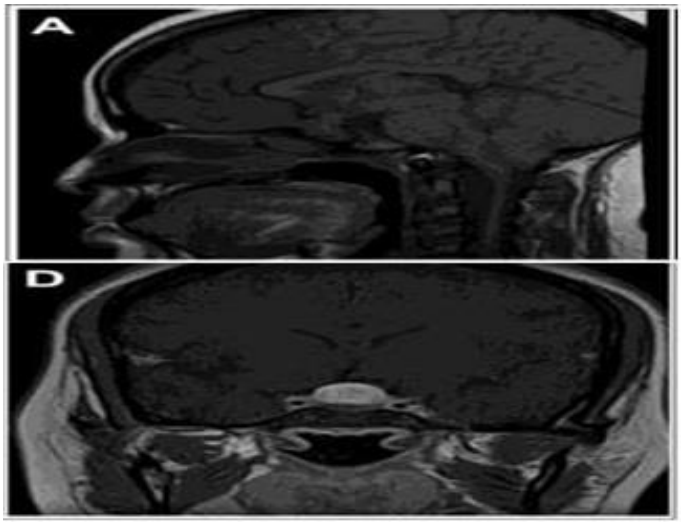

Figure (5): MRI showing pituitary gland enlargement in ipilimumab induced hypophysitis [15]

Management of pituitary irAEs.

Ill patients are initially treated with high dose hydrocortisone intravenously, and then converted to oral glucocorticoid replacement when stable. High-dose corticosteroids do not enhance the improvement of the endocrine condition, actually it has been related to worse outcomes. [15] However it plays a key role in prevention of chiasmal compression in patients with greatly expanded pituitary gland. Therefore, Replacement dosages of oral glucocorticoids, such as low-dose prednisolone, could be used to treat clinically stable people with cortisol insufficiency. [16]

If hypophysitis is known, Secondary hypothyroidism can be diagnosed when a low TSH level is present in the presence of low or normal free thyroxine 4 (T4) and free thyroxine 3 (FT3) levels (T3). It's worth noting that levothyroxine medication should only be considered once hypocortisolism has been ruled out. Because it can be difficult to distinguish between sick euthyroid state and secondary hypothyroidism, especially in ill individuals with cancer or other irAEs, clinical correlation is important. [12]

Further hormone replacement therapies is administered as needed, as in **figure (6).** Estrogen or Testosterone could be provided if needed. Replacement of Growth hormone is not recommended due to the malignancy nature. A recovery of thyroid axis and gonadotrophins after treatment withdrawal were reported, while secondary adrenal insufficiency usually persists.[17]

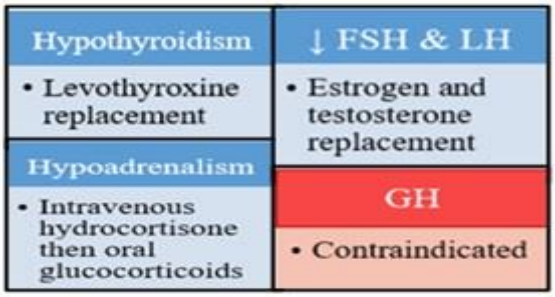

Figure (6): Hormone replacement therapy in hypophysitis [17]

5. Thyroid dysfunction associated with ICIs

The endocrine organ that is mostly affected by ICIs therapy is the thyroid gland. Which occur predominantly after PD-1 and CTLA inhibitors in combination, followed by PD-1/PDL-1 monotherapy.[9]

Both hyperthyroidism and hypothyroidism are reported,caused by an immune mediated thyroiditis. Hyperthyroidism is usually transient and occurs early in the treatment, However this is not universal, it is linked to a higher risk of future hypothyroidism.[18] Hypothyroidism may develop after hyperthyroidism, which is frequent, or it can develop alone.[19]

Assessment of thyroid irAEs

In thyroid irAEs the number of patients with positive thyroid peroxidase antibodies is much lower than in Hashimoto's thyroiditis. Thyroid autoimmunity, as evidenced by positive thyroid autoantibodies, is linked to ICI-induced thyroid dysfunction.[20] According to several studies, a higher TSH level at the beginning indicates subsequent thyroid dysfunction subsequent. [21] Graves' illness and thyroid eye disease can

develop together or separately in some cases, as its shown in **figure (7),** Often in patients who have been given CTLA-4 inhibitor Ipilimumab. With reported increase in iodine or technetium uptake in those patient.[22]

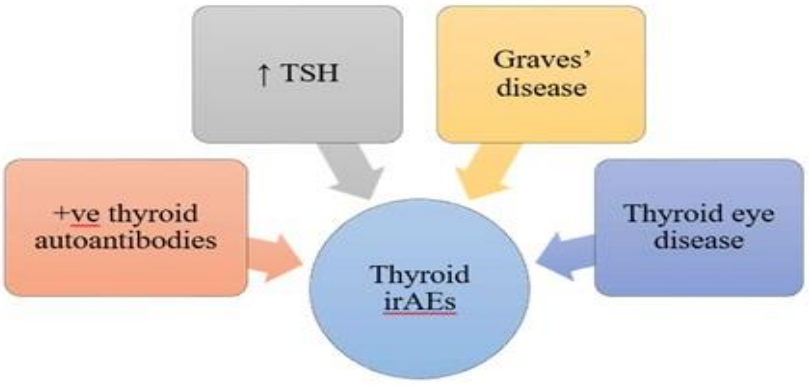

Figure (7): Thyroid irAEs clinical and laboratory correlations[20,21,22]

thyroid irAEs

Antithyroid medications are rarely needed considered in hyperthyroidism, and while guidelines encourage using beta blockers in patients with symptoms, antithyroid medications can be useful in circumstances when Graves' disease is suspected, such as when orbitopathy or persistent thyrotoxicosis are present. Glucocorticoids may be required in the rare case of painful thyroiditis. Whereas hyperthyroidism frequently progresses to hypothyroidism, there have been cases where people who were given glucocorticoids for other reasons did not proceed.[23] High-dose glucocorticoid treatment may be needed in patients who develop significant orbitopathy as a consequence of Graves' disease. Whears Thyroiditis and Graves' disease are mainly distinguished by their clinical appearance and temporal course. TSH receptor antibodies, doppler ultrasonography, and technetium uptake possibly have an impact in some patients. [21]

Guidelines recommend treating hypothyroidism with levothyroxine replacement in the same way as sporadic thyroid illness is treated, with medication in the case of a low T4 or a consistently elevated TSH more than two times the upper border of normal. Recovery appears to be a rare occurrence once clinically overt hypothyroidism has been detected. [24]

In most cases of thyroid irAEs, ICI medication should not be stopped; however, in severe thyrotoxicosis and severe thyroid eye illness, treatment suspension may be considered. Once hypothyroidism has developed, follow-up should be equal to the other types of hypothyroidism, and specialized endocrine involvement for uncomplicated hypothyroidism may not be required. [25]

6. Pancreas dysfunction associated with ICIs

ICIs-associated with pancreatic dysfunction can affect both endocrine and exocrine pancreas, leading to nutritional and metabolic disorders. Pancreatic irAEs include pancreatitis, hyperglycemia, elevated amylase/lipase, and exocrine pancreatic insufficiency, with a relatively low incidence rate. Patients treated

with ICIs mainly present with vomiting, abdominal pain, dyspepsia, irregular stools, and large daily glucose fluctuations. [26] After initiation of immunotherapy there is three to eleven weeks interval before the onset of ICIs associated with diabetes mellitus (ICIs-DM), and mostly in patients without pre-existing type 2 diabetes mellitus (T2DM). [27]

ICIs administration notably alter blood glucose level in cancer patients. HbA1C may be near normal or slightly elevated, C-peptide is low or undetectable, and in severe cases diabetic ketoacidosis were reported (DKA). [28] Patients with pre-existing T2DM may present with rapid hyperglycemia. Most ICIs-DM cases are observed during treatment with PD-1/PD-L1 inhibitors alone or in combination with other immunotherapies. [29] ICIs-DM are classified into four types, as its shown in **figure (8).** [26] This classification depend on the different clinical and biological profiles of ICIs-DM and their potential pathophysiology, as its described in **table (2).** [30]

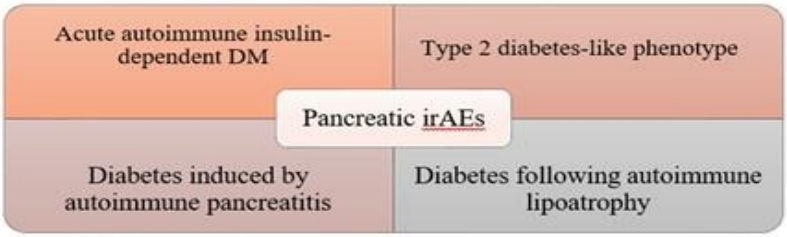

Figure (8): ICIs-DM classifications [26]

Table (2): ICIs-DM characteristic and pathology. [30]

Type	Characteristics	Possible mechanism
Acute autoimmune insulin dependent	Hyperglycemia, DKA, undetectable C-peptide and autoantibodies	1- B-cells be destroyed by CD8+ T cells, but a-cells are not affected. 2- The period of onset hyperglycemia may linked to the antibodies
Type 2 diabetes- like phenotype	Hyperglycemia, pre-existing T2DM, higher BMI, older age, hypertension, detectable C- peptide, higher HbA1c and CRP	1- B-cells be destroyed by CD8+ T cells, but a-cells are not affected. 2- T2D-like phenotype can be an insidious side effect on glycemia due to an abnormal chronic subclinical inflammatory state induced by long-term ICls therapy
Diabetes induced by autoimmune pancreatitis	Hyperglycemia, Higher HbA1c, pancreatitis and pancreatic atrophy	1- CD8+ T cells infiltrate in and around the pancreatic islets rather than CD4+ T cells. 2- It cause damage to pancreatic cells, including islet B-cells and acinar, thereby destroying exocrine and endocrine pancreatic tissues and resulting in pancreatitis-related diabetes and pancreatic atrophy
Diabetes following autoimmune lipoatrophy	Hyperglycemia, central obesity, higher HbA1c	1- The histological analysis revealed CD3+ T cells infitration and extensive fibroelastosis replacement. 2- The worsening of glycemic control is primarily related to the increased IR and concomitant with the progression of autoimmune lipoatrophy.

Acute autoimmune insulin-dependent DM

In this type the onset of diabetes mellitus (DM) is associated with autoimmune destruction of insulin-secreting β-cells. Mainly by CD8+ T cell clones promoted by blocking either PD-1 or PD-L1. [31] Presence of autoantibodies against β-cells will result in progressive insulinopenia, and onset of type 1 diabetes mellitus (T1DM). The period between start of ICIs therapy and onset of T1DM is has been related to the presence or absence of GAD antibodies (GADA). Patients with pre-existing positive GAD antibodies have higher risk of developing T1DM in the first two months after initiation of treatment. While in GADA-negative effect becomes evident after 2 months of treatment [32].

Type 2 diabetes like phenotype

After initiation of treatment with ICIs, Patients with type 2 insulin independent diabetes mellitus have a significant increase in blood glucose, as ICIs decompensates glucose control. Most of the patients are known to have a high body mass index (BMI), old age, hypertensive, with detectable C-peptide, and higher HbA1c in comparison to patients with acute autoimmune insulin-dependent DM. However laboratory findings of some patient revealed increased C-reactive protein (CRP) [31]. CRP levels are related to decrease insulin sensitivity, therefore chronic subclinical inflammation will lead to the development of insulin resistance (IR). Thus T2D-like phenotype is a gradual adverse effect of hyperglycemia featuring an abnormal inflammatory state induced by long-term use ICIs therapy. [33]

Diabetes induced by autoimmune pancreatitis

Patients with new-onset DM evolved autoimmune pancreatitis after immunotherapy. The activation of CD8+ T cell instead of CD4+ T cells is promoted by immunotherapy. Then it penetrates in and around pancreatic islets. This phenomenon demonstrates the development of pancreatitis and increase in pancreatic volume proceeding the onset of diabetes. Increased CD8+ T cells may injure pancreatic cells, including both islet β-cells and acinar, therefore demolishing exocrine and endocrine pancreatic tissues leading to pancreatitis-related diabetes plus pancreatic atrophy. [34]

Diabetes following autoimmune lipoatrophy

Autoimmune lipoatrophy also named acquired generalized lipodystrophy. Causes considerable decrease in whole-body fat. Lack of adipocytes promotes ectopic lipid droplet cumulating in other body parts. Atypical adipose storage is usually associated with the development of insulin resistance and DM. [35]

Management of diabetes irAEs

Given the prompt onset of insulin deficiency reported, all severely ill patients taking ICI should have regular checkup of plasma glucose, with urgent evaluation of ketosis and acidosis if hyperglycemia is noted. DKA should be treated with standard approaches. While patient with new onset hyperglycemia without DKA can start subcutaneous insulin. [36] As any newly diagnosed diabetes insulin treatment is required, before discharge patients must have a safe system of insulin injections on a regular basis. Patients should then consult an endocrinologist, and initial education should be provided by a diabetes specialist nurse. This is especially significant

because patients may be given glucocorticoids, which will likely worsen hyperglycemia. The ICI should be continued once glucose levels are under control, according to most guidelines. [37]

7-Conclusion

Immune checkpoint inhibitors immunotherapy has become more prevalent in the treatment of cancer. It boosts the immune system's capability to reach malignant cells efficiently, thus limiting tumor growth. However it has been associated with the emergence of new onset endocrine dysfunction. Pituitary and thyroid gland are generally more involved giving the picture of pan-hypopituitarism and hyperthyroidism followed by hypothyroidism respectively. Both exocrine and endocrine pancreatic dysfunction was observed. Presented by diabetes mellitus as an endocrinal dysfunction, endocrinologists should be aware of the arousal of the sign and symptoms of ICIs with prompt management. Patient who does not regain normal endocrine function must take lifelong hormonal replacement therapy under the supervision of specialist.

8. Recommendations

1- Endocrinologists need to be aware of the symptoms and signs of immunotherapy adverse effects to ensure early identification of possibly serious but curable cancer therapy negative effects.

2- Patients that are getting cancer immunotherapy should have regular laboratory checkup in aim of early diagnosis and management.

3- Patients should be educated to report any new symptom after the initiation of treatment to help in early recognition and prevention of the possible side effect.

4- Psychological aspect of the patient should be considered with psychiatrist consultation if required as it may affect the quality of life of the patient.

Acknowledgment

First and foremost thanks are due to ALLAH, to whom I relate my success in achieving any work in my life. I would like to express my deep and sincere gratitude to **Dr. Ashraf Shoma,** Professor of surgery and dean faculty of medicine in Mansoura University**. Dr. Ahmed Negm,** Professor of surgery, Mansoura Manchester program's director and **Dr. Emad shawky** consultant of nephrology, Mansoura Manchester program's phase director for providing us with this opportunity to do this essay.I am extending my thanks for my supervisor **Dr. Hanan Abdulhay** for her support, help and for providing valuable guidance through this essay. A special thanks to **MMPME** for funding this work and the valuable assistance throughout its conduct. Finally I wish to thank my family for their love, prayers, caring and sacrifices for educating and preparing me for my future.

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