Journal of Clinical and Translational Endocrinology: Case Reports 13 (2019) 100052

Contents lists available at ScienceDirect

Journal of Clinical and Translational Endocrinology: Case Reports

journal homepage: www.elsevier.com/locate/jctecasereports.com

A case of gynecomastia from a βhCG secreting bladder tumour

Kathrine Lee-A-Ping[a,b], Jimmy Li Voon Chong[c]

[a] Foundation Year 1 Doctor at Great Western Hospitals NSH Foundation Trust, Swindon, UK
[b] St. George's University, Grenada
[c] Consultant Endocrinologist at the Royal Hampshire County Hospital, Winchester, UK

ARTICLE INFO

Keywords:
Gynecomastia
Human chorionic gonadotropin
Beta subunit
Urothelial carcinoma
Prognosis

ABSTRACT

Background: Beta human chorionic gonadotropin (βhCG) is a glycoprotein secreted by trophoblastic cells during gestation. Various solid epithelial cancers can raise levels of βhCG and can cause gynecomastia. There are a few case reports that show elevated levels of βhCG especially in the context of transitional cell carcinoma (TCC) of the bladder to have a much poorer prognosis. In addition, these cases were found to have more aggressive disease and a higher likelihood of metastasis. There is little evidence in the literature regarding the work up of gynecomastia in adolescent patients and whether all gynecomastia workups should have a βhCG evaluation.
Results: An otherwise fit and healthy 71-year-old male presented with bilateral gynecomastia, breast pain and significant weight loss. He was investigated by the breast surgeons who ruled out breast malignancy. He was then referred to the endocrine department for further investigations and was found to have hypogonadism with a significantly raised βhCG. In view of the raised βhCG, computed tomography (CT) scan of the chest, abdomen and pelvis was performed to look for any underlying tumour. This showed a large bladder tumour, and biopsy of the mass confirmed the diagnosis of Ta 4NxM1 sarcomatoid bladder tumour.
Conclusion: Raised βhCG level in a patient with gynecomastia could be due to an underlying transitional cell carcinoma of the bladder. Therefore, any raised βhCG level warrants further investigation.

Gynecomastia is defined as a benign proliferation of glandular breast tissue in men [1]. Gynecomastia can be idiopathic or have several pathological causes [3]. A common cause is a suggested imbalance in male and female sex hormones favouring the circulation of oestrogens as oestrogen stimulates the growth of breast tissue [3]. Gynecomastia can occur in infancy, adolescence and adulthood typically among the elderly but usually it is benign and spontaneously resolves when it occurs in infancy and adolescence. The reported prevalence is 32–65% but depends on the criteria used for definition [4]. The prevalence of adolescent onset gynecomastia with a peak incidence between 13 and 14 years occurs in 40–65% of cases [5]. However, as it can be the first symptom of underlying pathology, gynecomastia of adulthood warrants proper investigation as there may be an underlying pathology in 45–50% of cases [1].

There is little evidence and controversy in the literature regarding the work up of gynecomastia in adolescent patients [1] and whether all gynecomastia workups should have a βhCG evaluation. The purpose of a gynecomastia workup should be to detect any reversible causes, underlying pathological conditions and discriminate breast lumps from breast cancer [4].

This paper presents an unusual case of an βhCG secreting tumour leading to gynecomastia. βhCG is a heterodimeric glycoprotein with regulatory roles dealing with the placenta, uterus and foetus and is released during gestation by trophoblastic cells [2]. Serum βhCG is therefore a key tumour marker of trophoblastic disease [6].

There is evidence that βhCG can facilitate angiogenesis via the transforming growth factor beta pathway [7]. There is also evidence showing that βhCG expression by TCCs indicated dedifferentiation towards a gestational trophoblastic phenotype and these particular tumours are usually poorly differentiated (R. K. [8]. Various studies show that tumours stained with squamous metaplasia, βhCG and a combination of both, have very poor response to radiotherapy whereas tumours without either of these features do respond to treatment [9].

As βhCG can be secreted from tumours and also be a cause of gynecomastia, patients with gynecomastia need to have their βhCG level checked and if it is raised, this should trigger a search for an underlying tumour.

1. The case

1.1. Patient information

A 71-year-old normally fit male presented with a 6-month history of enlarging breasts and pain over the nipples. He had an unremarkable

E-mail address: kathrine.leeaping@yahoo.com (K. Lee-A-Ping).

https://doi.org/10.1016/j.jecr.2019.100052
Received 20 February 2019; Received in revised form 16 July 2019; Accepted 19 July 2019
2214-6245/ Crown Copyright © 2019 Published by Elsevier Inc. This is an open access article under the OGL license (http://creativecommons.org/licenses/OGL/3.0/).

past medical history and non-contributory family medical history. His only medications included over-the-counter antihistamines. He was a non-smoker and drank minimal alcohol.

1.2. Timeline

In July 2016 the patient was seen by the breast surgeons. The initial investigations carried out including ultrasound scan of the breasts and testes showed no abnormalities. Blood results from this time can be seen in Table 1 of the Appendix. Clinical examination showed the patient had bilateral gynecomastia with tenderness over the areolas. The breastplate on the right was slightly larger at 4 cm compared with the left at 3 cm. The patient noted no itchiness, discharge or lumps. His initial blood tests showed raised 17 estradiol and reduced LH and FSH. His alpha-fetoprotein was normal and beta-hCG was pending. In light of the patient's abnormal oestrogen levels, he was referred to the Endocrine department.

The patient attended Endocrine clinic in August 2016. By this time, his beta-hCG results were 679 iu/L (N 0–5). He also reported weight loss of seven pounds over the previous month, slightly reduced appetite but no pain or nausea. Clinical examination revealed a blood pressure of 160/70, weight of 83 kg, BMI of 24, bilateral gynecomastia with diffuse breast plates, no lymphadenopathy or organomegaly. Examination of the genitals showed normal testicles. Examination of the other systems was unremarkable. A CT scan of the chest, abdomen and pelvis (CT CAP) was then organised for the patient to search for any underlying malignancy to explain the significantly raised hCG.

In September 2016, the results of the CT chest abdomen pelvis as shown inFigs. 3 and 4 of the Appendix, showed a huge right sided bladder tumour extending beyond the bladder with gross hydronephrosis on the right. There was no obvious infiltration into adjacent bowels but there were metastatic lesions in left and right upper lobes of the lungs. The patient reported haematuria in August 2016 and was referred to the Haematuria clinic. At that point, a cystoscopy was performed, and a few biopsies were taken of a necrotic solid tumour on the right wall which confirmed a T4NxM1 sarcomatoid bladder tumour.

In October 2016, the patient was then seen by the urologist in clinic. He was admitted for a cystoscopy under general anaesthesia which was a follow up from the flexible cystoscopy carried out earlier from which biopsies were taken which showed spindle cell urothelial cancer. At this procedure, the bladder was washed out and no further biopsies were taken. This was then followed up by the patient returning for a nephrostomy to be fitted on the right, due to hydronephrosis (seen on CT scan). Later in October, the patient was seen in Urology clinic and was then referred to an oncologist in a local tertiary centre following a multidisciplinary team (MDT) discussion. A few days later, the patient was admitted to the hospital with acute urinary retention and a urinary tract infection (UTI). On this admission he was catheterised and treated with intravenous (IV) antibiotics. In November 2016, the patient was seen by an oncologist and was started on palliative chemotherapy with carboplatin and gemcitabine.

The patient subsequently became unwell and was admitted to the University Hospital of Southampton in December 2016 with neutropenic sepsis, pancytopenia, vomiting, decreased oral intake and

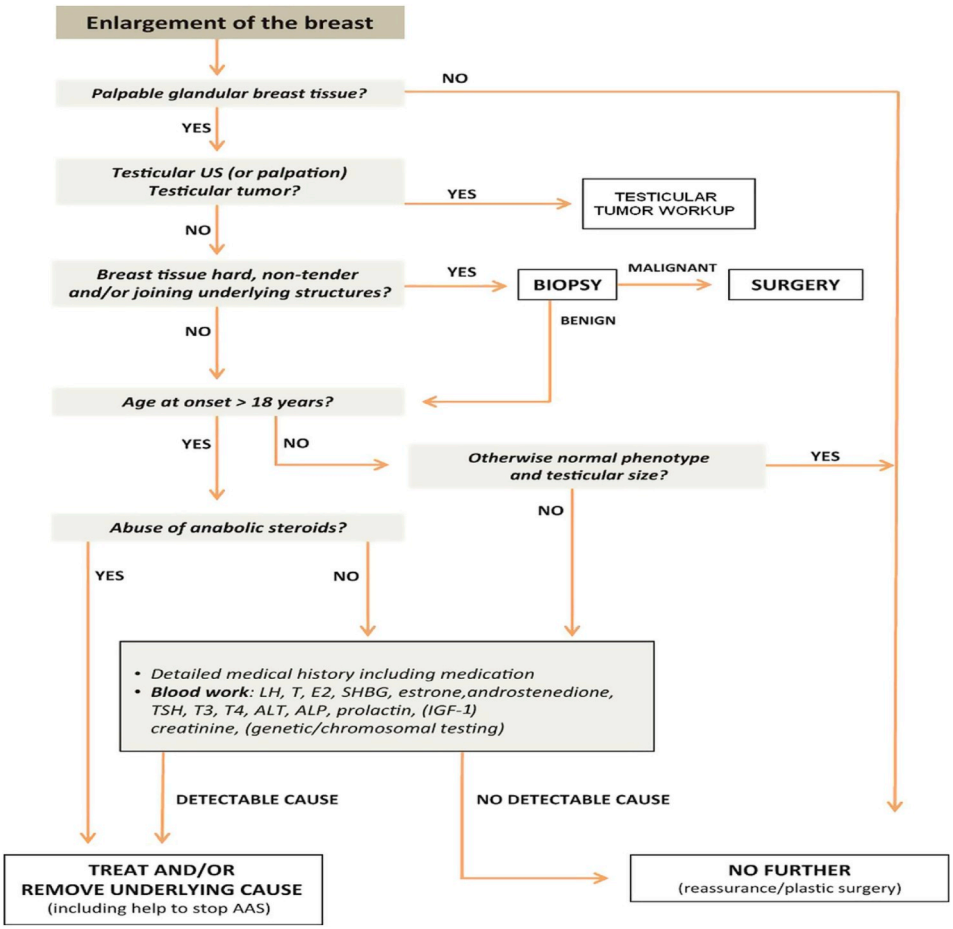

Fig. 1. Flow chart displaying a comprehensible clinical and biochemical work-up of adult men presenting with breast development. Reprinted from *Gynecomastia in 786 adult men: clinical and biochemical findings*, by European Journal of Endocrinology, May 2017, retrieved from https://eje.bioscientifica.com/view/journals/eje/176/5/555.xml Copyright 2017 by European Society of Endocrinology.

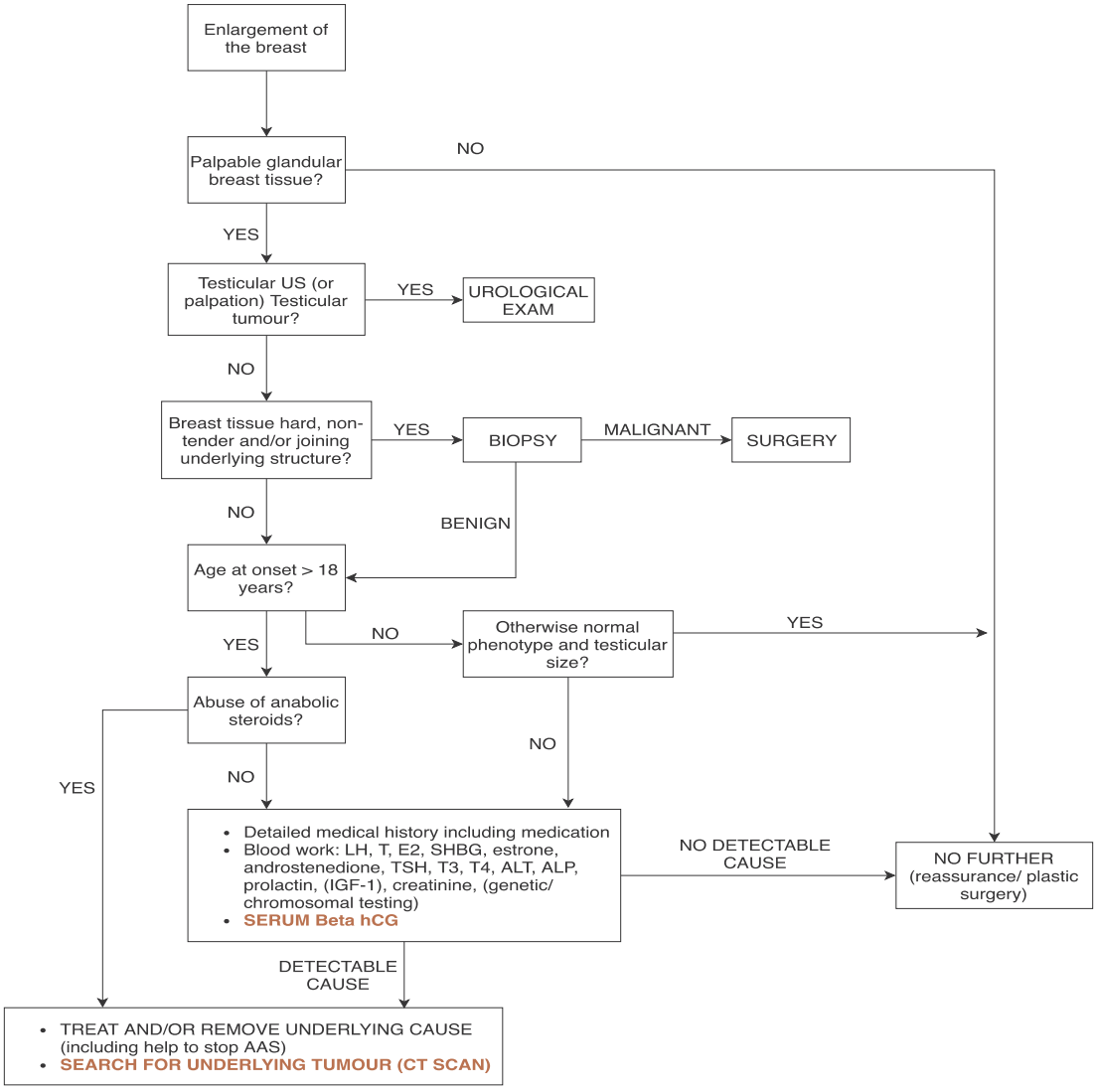

Fig. 2. Flow chart displaying a comprehensible clinical and biochemical work-up of adult men presenting with breast development with the authors' recommendation to include serum βhCG as part of the endocrinologic work up. Adapted from *Gynecomastia in 786 adult men: clinical and biochemical findings*, by European Journal of Endocrinology, May 2017, retrieved from https://eje.bioscientifica.com/view/journals/eje/176/5/555.xml Copyright 2017 by European Society of Endocrinology.

acute kidney injury (AKI). Blood cultures taken demonstrated *Bacteroides fragilis*. The patient was treated with antibiotics, granulocyte colony stimulating factor, IV fluids and a blood transfusion. CT CAP was done and showed a new right pelvic wall collection contiguous with the bladder and involving the right obturator internus muscle, a new but mild left hydronephrosis and progressive disease in the lungs with new and enlarging pulmonary nodules. In light of his malignancy, not much could be done for the patient and the decision was made to manage his symptoms palliatively. Blood results from January 2017 can be seen in Table 1 of the Appendix. He was transferred to a hospice centre and later passed away in February 2017.

2. Discussion

This case report was undertaken retrospectively with informed consent being obtained from the patient's widow. This case presents a 71-year-old male patient presenting with gynecomastia and absent urological symptoms who was subsequently found to have an elevated level of βhCG. In any adult, male patient presenting with elevated βhCG, a testicular ultrasound scan is the investigation of choice which was done for this patient on his presentation. However, this patient's testicular ultrasound was negative, and this proved to be an unusual case of an aggressive transitional cell carcinoma of the bladder that secreted high levels of βhCG.

Ectopic expressions of βhCG is now a recognized and well-documented phenomenon in many epithelial carcinomas arising from mucosal epithelial which include the lung, cervix and naso-pharynx (R. K. [8]. Elevated levels of βhCG can also be seen in other solid tumours including transitional cell carcinoma (TCC), prostate adenocarcinoma and urothelial cancer, and high levels are linked to a poorer prognosis [10]. Despite knowing that ectopic βhCG has been observed in different types of malignancies including TCC, levels of βhCG are seldom monitored in cases of TCC of the bladder [7].

βhCG increases cell populations by inhibiting apoptosis [7]. It was

discovered that addition of βhCG beta to the culture media of bladder, cervical and endometrial carcinoma cells lines brought about an increase in the rate of replication [11]. Ectopic productions of βhCG contributes to radio-resistance and metastatic potential of such secreting tumours [12,14]. Serum total βhCG level is an independent prognostic factor in patients receiving chemotherapy for urothelial TCC in both curative and palliative settings [13]. Patients with high levels of βhCG have a higher grade of malignancy and poor histological differentiation in addition to less favourable outcomes [12].

Gynecomastia can be caused by βhCG producing tumours including testicular tumours, adrenocortical tumours, lung cancer, gastric carcinoma and renal carcinoma [6]. There is much controversy surrounding the workup of gynecomastia but there have been recent guidelines "EAA clinical practice guidelines—gynecomastia evaluation and management" published by the American Society of Andrology and European Academy of Andrology. Fig. 1 shows an algorithm for the workup of gynecomastia released by Ref. [1] in the European Journal of Endocrinology in 2017. Fig. 2 shows the algorithm by Ref. [1] with the authors' additional suggestions based on the case presented in this paper.

3. Conclusion

All patients with pre-pubertal onset of gynecomastia and those with gynecomastia who exhibit signs of endocrinopathies should be given a formal endocrinologic evaluation [5]. The. Authors recommend that endocrinological evaluation of gynecomastia should be inclusive of serum βhCG levels. For adolescents with gynecomastia, routine endocrinologic investigations are not warranted as they provide a low-yield component in the diagnostic algorithm and they are unnecessary testing for the patient with a high case-cost burden [5].

Despite the novelty of this case report, it has significant importance in the wide range of medical knowledge. This case shows that medical specialists should always keep in mind the potential aetiology of bladder cancer in cases of raised βhCG levels and check serum βhCG levels in cases of gynecomastia.

Financing

No form of financing was required in the undertaking of this project.

Conflict of interest statement by authors

There was no evidence of any conflict of interest in the undertaking of this project.

Contributing authors

Kathrine Lee-A-Ping, Jimmy Li Voon Chong.

Acknowledgements

We would like acknowledge Hayden Nanton for his editorial contribution and invaluable assistance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jecr.2019.100052.

Appendix

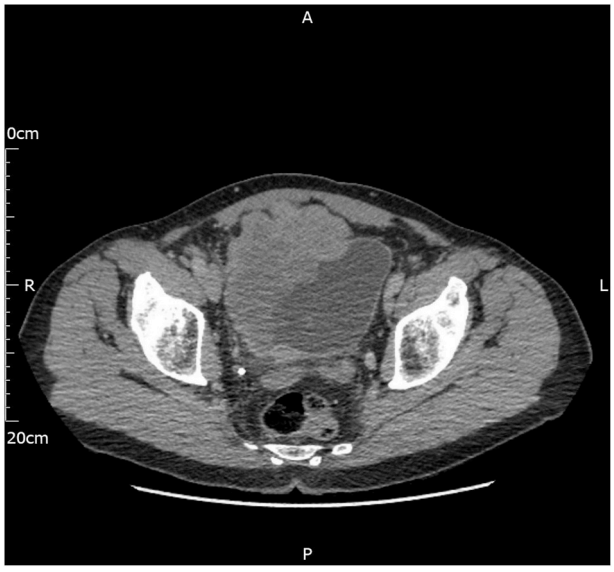

Fig. 3. Axial CT of the Patient Showing a Large Right Sided Bladder Tumour Extending Beyond the Bladder with Gross Hydronephrosis on the Right Side. No Obvious Infiltration into Adjacent Bowels.

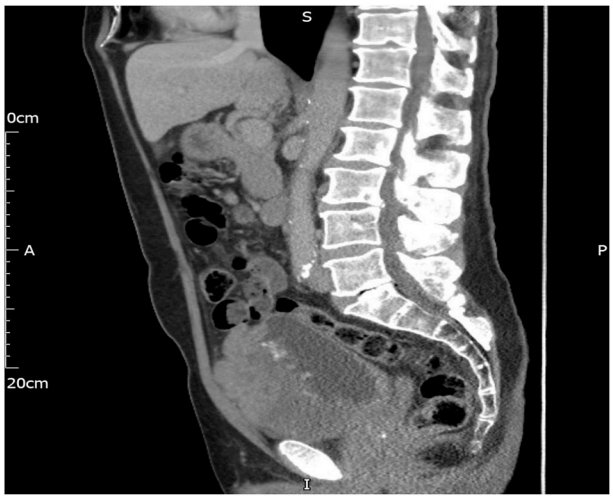

Fig. 4. Sagittal CT of the Patient Showing a Large Right Sided Bladder Tumour Extending Beyond the Bladder with Gross Hydronephrosis on the Right Side. No Obvious Infiltration into Adjacent Bowels.

Table 1
Table Showing Patient's Blood Results from July 2016 and January 2017.

Bloods	July 2016	January 2017	Normal Reference Range
Haemoglobin	133	77	130–180 g/L
White Blood Cell Count	–	12.8	4–11 10^9/L
Prothrombin Time	–	15.2	11.6–13.9 s
APTT	–	60.5	24.5–37.1 s
Bilirubin	8	4	0–21 μmol/L
ALT	12	11	0–60 U/L
Alkaline Phosphatase	79	78	46–116 U/L
Albumin	38	16	35–50 g/L
Free T4	17.2		11–23 pmol/L
TSH	0.81	–	0.35–4.5
Sodium	139	125	133–146 mmol/L
Potassium	4.7	Specimen haemolysed	3.5–5.3 mmol/L
Urea	8.1	14.5	2.5–7.8 mmol/L
Creatinine	99	330	62–115 μmol/L
eGFR	75	15	60–99 999 mls/min
FSH	< 0.3	–	1–18 u/L
LH	< 0.3	–	2–9 u/L
Sex hormone binding globulin	64	–	10–70 nmol/L
Total testosterone	14.7	–	10–35 nmol/L
Free testosterone	280	–	225–99 999 pmol/L
Prolactin	148	–	45–375 mu/L
17 Oestradiol	236	–	0–146 pmol/L
PSA	2.8	–	0–5 μg/L
Alpha fetoprotein	2.3	–	0–10 kU/L
βhCG	679	–	0–5 iU/L
C-reactive Protein	–	157	0–5 mg/L

Note: Results were obtained from the patient's National Health Service electronic medical record with consent from the patient's widow.

References

[1] Mieritz MG, Christiansen P, Jensen MB, Joensen UN, Nordkap L, Olesen IA, ... Jorgensen N. Gynaecomastia in 786 adult men: clinical and biochemical findings. Eur J Endocrinol 2017;176(5):555–66https://doi.org/10.1530/EJE-16-0643.
[2] Douglas J, Sharp A, Chau C, Head J, Drake T, Wheater M, ... Crabb SJ. Serum total hCGβ level is an independent prognostic factor in transitional cell carcinoma of the urothelial tract. Br J Canc 2014;110(7):1759–66https://doi.org/10.1038/bjc.2014.89.
[3] Park SH, Kim JH, Choi HJ, Lee YM. aaps 2017;23(2):101–3.
[4] Kanakis GA, Nordkap L, Bang AK, Calogero AE, Bártfai G, Corona G, ... Jørgensen N. EAA clinical practice guidelines—gynecomastia evaluation and management. Andrology 2019(1):1–16https://doi.org/10.1111/andr.12636.
[5] Malhotra AK, Amed S, Bucevska M, Bush KL, Arneja JS. Do adolescents with gynecomastia require routine evaluation by endocrinology? Plast Reconstr Surg 2018;142(1):9e–16ehttps://doi.org/10.1097/PRS.0000000000004465.
[6] Hotakainen K, Lintula S, Jarvinen R, Paju A, Stenman J, Rintala E, Stenman U-H. Overexpression of human chorionic gonadotropin beta genes 3, 5 and 8 in tumor tissue and urinary cells of bladder cancer patients. Tumour Biol: J Int Soc Oncodevelopmental Biol Med 2007;28(1):52–6https://doi.org/10.1159/000097703.
[7] Yacur M, Ei M, Sulseki J, Jj D, Joshi M. Annals of carcinogenesis expression of Beta-Human Chorionic Gonadotropin (Beta-HCG) in transitional cell carcinoma. 2017;2(1):1–4.
[8] Iles RK. Ectopic hCGβ expression by epithelial cancer: malignant behaviour, metastasis and inhibition of tumor cell apoptosis. Mol Cell Endocrinol 2007;260–262:264–70https://doi.org/10.1016/J.MCE.2006.02.019.
[9] Jenkins BJ, Martin JE, Baithun SI, Zuk RJ, Oliver RTD, Blandy JP. Prediction of response to radiotherapy in invasive bladder cancer. Br J Urol 1990;65(4):345–8https://doi.org/10.1111/j.1464-410X.1990.tb14753.x.
[10] Venyo AKG, Herring D, Greenwood H, Maloney DJL. The expression of beta human chorionic gonadotrophin (beta-HCG) in human urothelial carcinoma. Pan African Med J 2010;7:1–16.

[11] Moutzouris G, Yannopoulos D, Barbatis C, Zaharok A, Theodorou CH. Is beta-human chorionic gonadotrophin production by transitional cell carcinoma of the bladder a marker of aggressive disease and resistance to radiotherapy? Br J Urol 1993;72(6):907–9https://doi.org/10.1111/j.1464-410X.1993.tb16294.x.

[12] Martin JE, Jenkins BJ, Zuk RJ, Oliver RTD, Baithun SI. Human chorionic gonadotrophin expression and histological findings as predictors of response to radiotherapy in carcinoma of the bladder. Virchows Arch A Pathol Anat Histopathol 1989;414(3):273–7https://doi.org/10.1007/BF00822032.

[13] Dirnhofer S, Koessler P, Ensinger C, Feichtinger H, Madersbacher S, Berger P. Production of trophoblastic hormones by transitional cell carcinoma of the bladder: association to tumor stage and grade. Hum Pathol 1998;29(4):377–82https://doi.org/10.1016/S0046-8177(98)90119-8.

[14] Iles R. β-hCG expression by bladder cancers. Br J Canc 1992;65(2):305https://doi.org/10.1038/bjc.1992.62.