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Prevalence, incidence, and risk of cancers in patients with acromegaly: review

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Abstract:
Introduction and purpose: Acromegaly is a relatively rare disease, with the incidence of 0.2 - 1.1 cases in 100 000 people per year. Increased secretion of growth hormone (GH) is the main pathomechanism. GH stimulates the liver to the insulin-like growth factor type 1 (IGF-1) production. It leads to the tissues overgrowth, facial changes, metabolic and cardiovascular comorbidities, such as diabetes, hyperthyroidism, or hypertension. The main aim of this review is to provide the most up to date knowledge about epidemiology and risk factors of neoplasms which occur more often in acromegaly, than in the general population.
State of knowledge: Some studies showed that substances from the IGF group – including IGF-1, have a cancerogenic effect on the cells. According to that fact, groups of acromegalic patients were examined in the search for cancers. Studies delivered that there is a higher chance of neoplasms in acromegalic patients. The most widely described cancers in the relation with this disease are: prostate cancer, breast cancer, thyroid cancer, and colon cancer. There are some neoplasms which have lesser number of studies, such as: renal cancer, neoplasms of the female reproductive system, haematological cancers as well as osteosarcoma.
Conclusions: Cancers occurs more frequently in acromegalic patients and have a major impact on patients' life-span. Early detection as well as quick provision with the adequate treatment is highly necessary for extending patients' lives.
Key words: acromegaly; neoplasms; prostate cancer; breast cancer; thyroid cancer; colon cancer

INTRODUCTION AND PURPOSE

Malignancies in acromegalic patients are more frequent in comparison to overall population [1]. Widening the knowledge in that subject can provide early cancer detection and urgent treatment. Not only will these actions improve patients' quality of lives but also prolong their lifespan.

Acromegaly is characterized by high growth hormone (GH) secretion, which then stimulates the liver to insulin-like growth factor I (IGF-1) production. Both these factors lead to tissues overgrowth. The most frequently occurring features in acromegaly are: hands and toes enlargement, facial changes such as increased size of jaw and nose, eyebrows enhancement, diastema, excessive sweating, heart overgrowth, colon polyps, constipation, diabetes and hyperthyroidism [2-4]. The most common cause of excessive GH serum level are pituitary macroadenomas. The other reasons of increased GH are: ectopic production of growth hormone releasing hormone (GHRH) by neuroendocrine tumour – mainly by pancreatic and bronchus neoplasm [5], as well as secretion of GH by non-pituitary tumours such as non-Hodgkin lymphoma [6]. The incidence of acromegaly is estimated for 0.2-1.1 cases per 100 000 people per year, however, it still remains underdiagnosed [7].

Studies revealed that changes in the GH/IGF-1 axis, especially higher levels of the IGF-1, are responsible for tissue overgrowth and can lead to the cancerogenesis [8]. The IGF-1 directly binds to its receptor (IGF-1R). That activates pathways such as: PI3K/AKT, MAP kinase or mTOR. All these cascades promote mitogenesis, cell cycle modifications as well as protection from apoptotic factors [9-11]. Subsequently, the IGF-1 increases synthesis of the cyclin D1, which accelerates the cell cycle and leads to the mitogenesis [12], [13]. Furthermore, the cyclin D1 is in control of some protooncogenes (such as c-FOS, c-JUN), has the antiapoptotic impact on the cells and modulates the immune response [14], [15].

There are many neoplasms which occur more frequently in acromegalic patients than in the general population. Tumours such as the prostate cancer, the breast cancer, the thyroid cancer and the colorectal cancer are well-described. However, due to the rarity of acromegaly many of neoplasms were not well examined. The aim of that report is to update current knowledge in the topic of epidemiology and pathogenesis of malignant cancers which appear in the acromegalic patients.

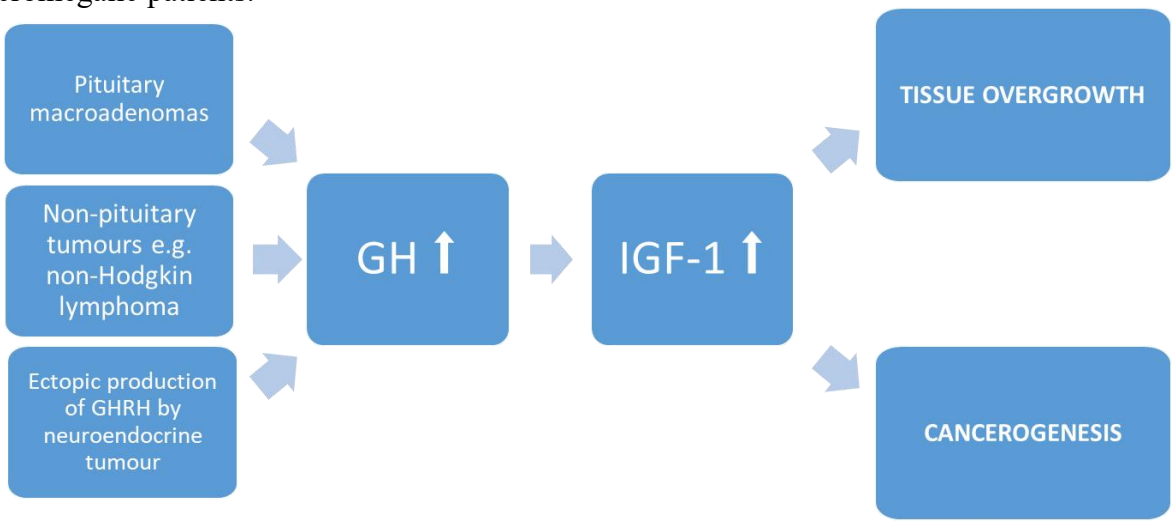

Fig. 1. Factors determining the pathophysiology of cancers in acromegaly.

RESULTS

Prostate cancer

Prostate cancer (PCa) as the second most frequent and fifth most deadly neoplasm amongst adult males worldwide [16], is a target of extensive research. The goals of the studies are the establishment of PCa risk factors and development of new therapeutic strategies. Acromegaly and higher activity of GH/IGF axis is well proven to be associated with higher rates of prostate-related events, in particular benign prostatic hyperplasia (BPH) and structural abnormalities such as nodules, cysts or micro- and macrocalcifications [17-21]. The hypothesis of acromegaly being associated with higher PCa incidence though wasn't verifiable until recently, due to relatively short lifespan of the individuals affected with acromegaly and high mean age of PCa onset. Nowadays patients with acromegaly are able to survive long enough to be enrolled in epidemiological studies.

In one of the first studies on the topic Madajewicz et al. in 1979 attempted the inducement of the GH release in 12 patients with PCa, which was achieved and maintained during the study in 3 patients. All of them subsequently presented with rapidly progressing disease which led to their death after no more than 5 months (2 patients after 2 months, one patient after 5 months) [22]. In the same year The British Prostate Study Group compared plasma concentrations of GH and other hormones among patients categorised according to UICC TNM classification. The GH values were observed to be significantly higher in M1 (metastases) group – mean 4.0 mU/l - compared with M0 (no metastases) group – mean 2.6 mU/l [23]. Approach of Mantzoros et al. was to study the effects of rising IGF-1 concentrations on BPH and PCa risk. No correlation regarding BPH was found, although PCa displayed an association with the hormone levels - an increase of 60ng/ml IGF-1 corresponded to higher PCa risk – odds ratio of 1.91 (95% CI 1.00-3.73) [24]. A year later Chan et al. observed similar results – patients from the group of highest quartile IGF-1 concentration had significantly higher risk of PCa development compared to the lowest quartile – relative risk of 4.3 (95% CO 1.8-10.6) [25]. In a study by Wolk et al. a 100ng/ml rise in IGF-1 was associated with higher PCa risk as well – odds ratio of 1.51 (95% CI 1.00-2.26), which was particularly pronounced in men above age of 70 – odds ratio was 2.93 (95% CI 1.43 – 5.97) [26]. In a more recent English national record linkage study the prevalence of PCa in 2495 acromegalic patients was compared to the reference cohort of 4.3 million men. The hazard ratio for PCa diagnosis in patients with acromegaly was 1.33 (95%CI 1.09-1.63) and for death associated with PCa it was 1.44 (95% CI 0.92-2.26) [27]. Dal et al. in 2018 conducted a cohort study and included the results in the meta-analysis of cancer standardized incidence ratios (SIR) from 22 other studies. The cohort study results showed a slightly higher PCa risk in acromegalic patients compared with the overall population rates (SIR 1.4, 95% CI 0.6-2.6). The meta-analysis stratification based by cancer type displayed pooled SIR of 1.2 (95% CI 0.8-1.9) for PCa [28].

On the contrary, there were some studies that resulted with lack of evidence on any influence of GH-IGF axis on PCa risk [19], [29-31], prostate specific antigen levels [32], or even displayed a positive impact of higher GH concentrations on PCa outcome. According to Torosian, higher GH levels protected tested animals from the loss of body weight, and inhibited pulmonary metastasis [33]. In Fuhrman et al. study the higher basal GH levels were associated with decreased prostate cancer risk (OR 0.35, 95% CI 0.12-1.05 in the highest quintile compared to the lowest) [34].

Despite that facts, due to the growing clinical evidence of acromegaly pathological influence on the prostate, a number of in vitro and animal studies were conducted in search of particular factors and mechanisms causing that effect. The disruption of GH signalling pathways or of its production in mice prostate carcinogenesis models resulted in the inhibition of the

progression of the benign, latent tissue to malignant state, decrease in cell proliferation and increase in apoptosis [35-38]. Results of in vitro studies confirmed GH as an important factor of PCa carcinogenesis, progression [39-42] and even aggressiveness and metastatic properties [43]. The in vitro [41, 44] and animal [35], [38], [45] studies concerning IGF displayed a similar effect on PCa development and progression to that of GH.

An indirect evidence for the association of acromegaly and GH/IGF axis may be the usage of the somatostatin analogues in PCa management, including castration-resistant tumours. The data from 42 studies with 267 castration-resistant PCa patients treated with somatostatin analogues alone or in the combination with other medications were gathered and analysed by Schmid et al. According to their 2008 systematic review the treatment was found to be effective (especially when used in the combination with steroids or estrogens) and not causing severe side effects [46].

Despite the studies, concerning the impact of acromegaly, GF and IGF on PCa development risk not proving acromegaly being the risk factor of that neoplasm unanimously, the clinicians should be aware of that risk – increased prostate state surveillance of individuals affected with acromegaly is strongly advised.

Breast cancer

As far as breast cancer is concerned, this is one of the most common types of malignant growth in acromegaly [1]. The reason for that seems to be higher concentration of IGF-I, as a result of excess production of GH [47]. This inflicts on proliferation of normal breast epithelium and subsequently, breast cancer may occur. IGF binding protein-3 (IGFBP-3) works as a restricting agent, limiting accessible IGF so that it cannot bind to its receptors, therefore limiting proliferation [47-52].

Hankinson et al. conducted a case-control study on 1017 women, with a control group of 620 and 397 cases of acromegaly, measuring plasma IGF-I and IGFBP-3 concentration. The study showed that in postmenopausal women there were no statistical significance of data, but in premenopausal women, the positive correlation was found, with relative risk of 2.65 (CI 95%, 1.04–6.75) [53]. Other authors lean towards the same hypothesis, with positive correlation being 2.05 (95% CI, 0.93-4.53) [54] and 2.30 (95% Cl 1.07-4.94) [55].

In meta-analysis by Renehan et al. confirmation was achieved that concentration of IGF-I and IGFBP-3 contributes to the risk of premenopausal breast cancer. The authors emphasize, however, that IGF-I level is energy-related and should not be considered only in relation to other risk factors such as: body-mass index, physical activity and growth in early life. Further studies should be conducted to confirm the correlation, which will allow the establishment of the reason why IGF-I specifically rises the chance of developing breast cancer [56].

Dal et al. in their cohort study, amid 261 female patients with acromegaly, observed 9 breast cancer cases that contributed to SIR of 1.1 (CI95%, 0.5–2.1). Aforementioned bias is present due to common screening programs, possible bad condition of patients and lack of sufficient control groups in smaller centres [1].

Thyroid carcinoma

Acromegalic patients demonstrate different benign proliferative lesions of thyroid such as: solitary nodule, simple goitre, multinodular goitre as well as malignant carcinomas. Thyroid cancers are one of the most frequent neoplastic comorbidities emerging in the course of acromegaly. The thyroid tumours show about 1.5-4 times more frequent prevalence in patients with acromegaly in comparison to the general population [57]. According to the data delivered by Kurimoto et al., the thyroid cancer was the second most common neoplasm (4.8 %) in a group of 87 acromegalic patients, while the first one was colon cancer (with the prevalence 10.3 %) [58]. The majority of studies prove that the approximate incidence of thyroid cancers is 3.1 %, but this number oscillates between 2.4 % up to 11 % [57], [59], [60]. What is noteworthy, the prevalence of thyroid neoplasms among patients with acromegaly is

comparable in males and females. [61] and the data show that there is no difference in the aggressiveness of thyroid carcinoma between patients with acromegaly and the control group [62].
Studies showed that 25% to 90 % of acromegalic patients manifested goitre and 65 % had multinodular goitre, which shows the positive correlation between the GH and IGF-1 levels and thyroid volume [62]. To understand the linkage between the thyroid benign and malignant nodules emergence in the course of acromegaly, the molecular aspects need to be highlighted. GH and IGF-1 are two factors, which are proven to have proliferative, mitogenic and antiapoptotic impact on thyroid follicular cells. In vitro studies were conducted on rat thyroid cells, which showed positive relationship between recombinant IGF-1 and mitotic division of TSH-induced cells. IGF-1 induces the thyroid cells proliferation indirectly through amplifying the effect of TSH on its function and development. Increased impact of TSH on thyroid cells may also result in nodular goitre formation and hyperthyroidism in the course of acromegaly [61].
Additionally, GH and IGF-1 influence the thyroid cells directly. Both normal and malignant thyroid cells were found to produce IGF-1 and to express IGF-1 receptors at once, which can be stimulated by GH. It also suggests the autocrine and paracrine action of IGF-1. This phenomenon has been proven by the studies, which showed high expression of IGF-1R, IGF-1, IGF-1R mRNA and IGF-1 mRNA in patients with thyroid carcinomas. Elevated levels of these factors were also found in nodular goitres and papillary adenomas, but not as high as in papillary thyroid cancers [57].
Some studies also emphasise that the hyperinsulinemia (often associated with increased body mass index [63]) is an additional condition contributing to more frequent cancer development in acromegaly. [57]. Other studies suggest that the consequences of acromegaly like pituitary irradiation, insulin resistance, leptin, obesity, high levels of IGF-BP1 and IGF-BP3 have also a possible impact on thyroid cancer formation [64].
While discussing the prevalence of thyroid carcinomas in acromegalics, it is important to mention that there is a risk of overdiagnosis in patients which are followed up frequently in the course of the disease. This methodological threat refers also to the fact that authors of some studies classified patients even with small thyroid nodules for cytology examination, resulting in thyroid microcarcinomas diagnoses, which are low-risk tumours [61], [62], [64] and would not be diagnosed in representatives of general population.

Colon cancer

A number of authors observed that acromegaly is connected with elevated risk of incidence of colonic polyps and colorectal cancer. [65-71] The largest meta-analysis from 2008 found a significantly increased risk of colorectal polyps (OR 3.6), colon adenomas (OR 2.5) and colon cancer (OR 4.3) among acromegalic patients [72]. However some authors, despite confirming the increased incidence of polyps, implied that there is no difference in the incidence of colorectal cancer between patients with acromegaly and the general population [61], [73]. These different opinions may result from the fact that the studies reported so far included a small number of samples and therefore they lacked adequate statistical power. While it is known that colorectal polyps are common in acromegalic patients, it is controversial whether these patients are at increased risk of colorectal cancer [73].
The high incidence of colorectal tumours in acromegaly is potentially attributed to the action of insulin-like growth factor (IGF-1), the secretion of which is stimulated by growth hormone (GH), a cell growth factor that can induce tumour growth [74].
Studies show that increased colon length (by 20%) [75] and increased incidence (37%) of colonic diverticula [76] are characteristic for patients with acromegaly. Ochiai et al. found significantly more polyps in the sigmoid colon and rectum in the acromegalic group than in the control group. Based on these reports, it can be concluded that the distance between the

sigmoid and rectum is particularly large in acromegalic patients, which makes them more likely to develop polyps than in the general population. [73]
Moreover, acromegaly is associated with increased proliferation of colon epithelial cells, which is associated with elevated levels of IGF-1 [77].
Taking into account epidemiological data, the current clinical guidelines recommend colonoscopy in patients diagnosed with acromegaly as well as during long-term surveillance in order to protect patients against colorectal cancer [78], [79].

Renal cancer

The first patient who suffered from acromegaly and developed a renal cancer (RC) was described in 1982, by Klein et al. [80]. Since that time some studies have been carried out which indicate the higher risk of the RC in patients with the acromegaly [81].
IGFs have stimulating effects on renal development during embryogenesis [82]. According to that phenomenon, some studies were conducted and showed that the high level of IGF-1 can lead to tumorigenesis in the organs which are typically reactive to the IGF-1, equally: kidney, thyroid and breast [83]. The IGF-1 binds to its receptors and activates the tyrosine kinase (TK) in the receptor. The TK stimulates the MAPK and phosphoinositol-3-kinase cascades which is responsible for mitogenesis, differentiation as well as inhibition of apoptosis [84]. Subsequently, the renal cell carcinoma is known for the IGF-1 production as well as the IGF receptor synthesis. This indicates the autocrine RC growth stimulation [85]. Furthermore, studies showed that the IGF-1R-negative renal clear cell carcinomas have higher survival ratio than the IGF-1R-positive [82].
The study by Blanck et al. was conducted on the Wistar rats. The recombinant human GH in the dosage of 2.5 IU/kg was injected subcutaneously. The results indicated that the most common venues of neoplastic formation were kidneys and liver. The higher number of the RC was observed in the female rats, however, survival ratio stayed on the same level [86].
In the study conducted by Jungwirth et al. the Caki-1 renal adenocarcinoma cell line was implied into the nude mice. The somatostatin analogue RC-160 was implied to the xenografts which led to the significant decrease of GH and IGF-1 levels. The results indicated clear antitumor actions on the renal adenocarcinoma [87]. The next study showed that 3 out of 7 mice xenografted by the RC which were treated with somatostatin analogue (AN-238) completely healed from the tumour [88].
The cohort study on 1213 Swedish and 421 Danish patients with acromegaly showed increased risk of the RC (SIR=3.2, 95% CI=1.6-5.5). The risk was incidental in women and men [89]. Another large-scale epidemiological study was conducted on the group of 1512 acromegalic Italian patients. The analysis revealed the higher rate of many neoplasms including the RC (SIR 2.87; 95% CI=1.55-5.34). Furthermore, the RC occurred more frequently in men [90]. The next epidemiological study was conducted on 333 Finish acromegalic patients over 15 years of age. Patients' histories were investigated respectively. Results indicated a significantly higher incidence ratio of urinary tract cancers (including RC) in the first 5 years of the observation (SIR 7.77, 95% CI=2.12-19.9) [91].
The hypertension as well as the obesity which occur in most patients with acromegaly are both risk factors of the RC. That can be also an explanation of the higher rate of the RC in people with that disease [89].
On the other hand, some studies did not prove the correlation between acromegaly and RC. There was the in vitro study on 20 human tumour models (including RC) delivered to the nude mice. The recombinant human GH was injected to the mice at concentrations of 0.3 ng/ml to 0.1 μg/ml. Results did not indicate any inhibition as well as stimulation of tumour growth [92]. The study conducted by Mehls et al. showed that in the group of 314 patients after renal transplantation who were treated with GH therapy only 3 developed RC. Results

indicated that the RC incidence was not increased in comparison to the general population [93].
Although there are some studies which showed the linkage between RC and acromegaly, there is still a wide range of strong evidence that RC is more frequent in these patients. Due to that fact, more studies are required to investigate the issue.

Cancers of female reproductive system

There are not many studies regarding the cancer risk of the female reproductive system in acromegaly. Some in vitro studies showed the correlation between higher IGF-1 and IGF-2 and the rise in cancer cell growth and aggressiveness, especially in ovarian cancer, although the results of meta-analyses on the topic didn't confirm that hypothesis in its entirety. The meta-analysis by Gianuzzi et al. regarding IGF, IGF-binding proteins and the risk of ovarian cancer evaluated the data from 14 case-control studies involving 8130 patients. IGF-1 levels turned out to be lower in patients with ovarian cancer, which suggested it's higher levels being a protective factor against cancer of ovaries (standardised mean difference: −0.43 ng/mL; 95% CI: (−0.67) – (−0.18)) [94]. Wang et al. explored the risk of ovarian cancer and its association with circulating IGF-1 levels in their meta-analysis as well – in 4 studies including 1985 patients, neither positive nor negative relationship was found (pooled odds ratio for highest vs lowest IGF-1 levels: 0.85; 95% CI 0.51-1.40) [95].
On the other hand, some retrospective epidemiological studies displayed the high occurrence of female reproductive system cancers in acromegalic patients. Nabarro described a personal series of 256 cases of acromegaly/gigantism, among which 26 developed malignancies. 2 patients were diagnosed with ovary cancer (0.8%) [96]. Amid 87 patients with acromegaly evaluated retrospectively by Barzilay et al. one developed ovarian cancer (1.1%) [97]. Popovic et al. reviewed clinical records of 220 acromegalic patients and found one ovarian carcinoma (0.4%) and four cervical carcinomas (1.8%) [98]. In a group of 101 patients with acromegaly studied by Baldys-Waligorska et al. cervical cancer was diagnosed in 3 patients, which made it the most frequent malignancy in this group (3.0%) [20]. Gullu et al. among clinical records of 105 acromegalic patients found one patient with cervical cancer (0.9%) [99].
Based on the existing evidence, it is not possible to conclusively state the existence of a correlation between the occurrence of acromegaly and a higher risk of the female reproductive system neoplasms.

Haematological neoplasms

Case reports and cohort studies show that haematological diseases diagnosed in the course of acromegaly include: polycythaemia vera, chronic myeloid or lymphocytic leukaemia, multiple myeloma (MM), lymphoma [100], [101]. The frequency of haematological malignancies is rather occasional, but noticeable. For example, one of the studies showed the prevalence of 3 haematological patients among 106 acromegaly patients in the period of 15 years [102]. Medical databases contain also a number of case reports describing haematological patients with acromegaly. According to some authors, despite lack of indisputable data showing the direct correlation between the acromegaly and the concomitance of haematological malignancies, this possible relationship cannot be ignored [100].
Analyses show the positive correlation between acromegaly and risk of leukaemia. This observation is supported also by the phenomenon of leukaemia recurrence in children who had survived childhood leukaemia and were treated afterwards with GH, as a prevention of GH deficiency. It turned out that in this group of patients, the risk of renewed leukaemia is much higher in the therapy with GH. This case demonstrates the strong relationship between leukaemia occurrence and GH/IGF-1 pathway [100].
Another mechanism is related with indirect GH action on the cells, including blood cells. GH stimulates both IGF-1 and IGFBP-3 (BP- binding protein) synthesis. IGF-1 is a factor causing

proliferation and mitogenic action of the cells, which directly increases the risk of malignancy. Oppositely, IGFBP-3 induces apoptosis and has an opposite effect to IGF-1. However, in the course of acromegaly, when the GH level is excessive, the IGF-1 to IGFBP-3 ratio is elevated resulting in increased risk of cancer or neoplasm, which may explain the possible tendency of haematological neoplasms in acromegaly [103].

In vivo and in vitro studies demonstrated the IGF-1 impact on lymphoid tissue through increased proliferation of CD4+ T cells and B cells. This process amplifies the synthesis of immunoglobulin, and development of MM. Different studies showed that human MM cells have IGF-1 mRNA receptors expressed on its surface, which enables IGF-1 to have a proliferative impact on the MM cells [103].

Despite the observations sketched above, the strong correlation between acromegaly and haematological malignancies is still unclear, both due to relatively rare incidence as well as lack of definite scientific evidence for this dependence.

Osteosarcoma

Only five cases of coexisting acromegaly and osteosarcoma were reported to this day. Chronologically first, a man at an age of 47 was diagnosed with acromegaly. Due to, remaining higher levels of the GH the alpha irradiation to the pituitary gland was conducted. Unfortunately, this procedure did not force any changes. The twelve years later during L4-L5 decompression laminectomy the tumour of the sacral canal was discovered. The microscopic evaluation confirmed the initial diagnosis of osteosarcoma [104].

The next two patients were young, acromegalic women who were treated by radiotherapy with progressive deteriorating state. Later osteosarcomas were found which developed on fibrous dysplasia base [105].

The fourth patient, a 72 years old man was diagnosed with acromegaly. He underwent transsphenoidal surgery of pituitary. The GH levels, however, remained elevated. Twelve years later the patient was diagnosed with osteosarcoma of the left and right femurs. The computed tomography imaging showed the lung metastasis. The patient obtained the palliative chemotherapy as well as radiotherapy. Unfortunately, the patient's state was worsening, leading to death a year later [106].

Fifth patient was a 39-year-old woman with a large left-sided mandibular mass, which was revealed to be osteosarcoma. After the operation the patient was subjected to diagnostics because of abnormal features typical for acromegaly. Elevated levels of pituitary hormones were confirmed along with brain MRI that resulted in pituitary tumour removal. Osteosarcoma tumour was analysed via immunohistochemistry, which showed presence of somatostatin receptor and IGF-2 receptor [107].

Despite the fact of using radiotherapy, reported patients lacked other predisposing factors of osteosarcoma, which are: chemical agents, ionizing radiation, alkylating agents, Paget's disease, hereditary disorders [108]. Therefore, attention of researchers was focused on GH and IGF-1/2 effect on tumour growth and aggressiveness. Due to the rarity of both conditions coexisting, there is a lack of sufficient evidence that acromegaly increases frequency of the osteosarcoma. Further studies on IGF molecules family should be conducted [109-111].

CONCLUSIONS

Acromegaly is the disease with many comorbidities such as cancers which has significant impact on patients' life-span. The most examined and described neoplasms occurring in acromegaly are prostate cancer, breast cancer, thyroid cancer and colon cancer. There are other neoplasms which are much more rare such as: renal cancer, female reproductive cancer, haematological cancers, as well as osteosarcomas. Acromegaly is a relatively rare disease. According to that fact, studies on the correlation between acromegaly and neoplasms are conducted on small groups of patients. Because of, the neoplasms are the major cause of deaths in patients with acromegaly further investigation on that topic is necessary [112].

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