Three secondary malignant neoplasms in a childhood cancer survivor positive for nibrin gene mutation – a case report and literature review

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Childhood cancer survivors often develop subsequent neoplasms secondary to radio- (RT) or chemotherapy (CHT). Risk factors for the secondary tumors are the female gender, older age at diagnosis, Hodgkin’s lymphoma treatment and the use of RT. The cumulative incidence of the second malignant neoplasm, excluding non-melanoma skin cancer, 30 years after the childhood cancer diagnosis is around 8% [1]. We present the case of a patient who developed three independent malignancies following radical treatment of nephroblastoma (Wilms’ tumor; WT) in childhood, found at the age of 53 to be a carrier of the 657_661delACAAA (p. Lys219fs) mutation in the 6/16 exon of the nibrin coding gene (NBN).

Key words: leiomyosarcoma, secondary neoplasms, radiotherapy, nibrin

Case report
A 52-year-old woman was diagnosed with hepatic hilum lymphadenopathy in November 2016. Past medical history of the patient included two metachronic neoplasms: WT with peritoneal infiltration at the age of six years treated with left nephrectomy followed by CHT with actinomycin D and left flank RT at the dose of 35.2 Gy, and grade III adenocarcinoma of the descending colon treated with left hemicolectomy at the age of 26 years. The family history was unremarkable.

At admission, physical examination was unremarkable. The patient’s performance status ECOG was 0. Magnetic resonance imaging (MR of 08.2016) showed the presence of a very small (11 x 13 mm) lymph node with low radiotracer uptake (SUV 2.1) at the positron emission tomography scan with 18-fluorodeoxyglucose. Six months later, MR showed a significant progression of the lesion (35 x 22 mm). The ultrasound-guided core-needle biopsy proved the diagnosis of a grade II leiomyosarcoma. In April 2017, the tumor originating from vena cava inferior was removed. Despite the presence of tumor cells in the resection margin adjuvant treatment was not administered due to the hemorrhagic complications and prolonged postoperative recovery. Eight months later, the patient was diagnosed with undifferentiated ovarian cancer, stage IA, and treated with radical surgery followed by 6 cycles of adjuvant CHT (carboplatin and paclitaxel).

Genetic testing after the diagnosis of sarcoma showed that the patient was a carrier of the 657_661delACAAA (p. Lys219fs) mutation in the 6/16 exon of the nibrin coding gene (NBN), uncommon in the Polish population. The leiomyosarcoma specimen examined for the presence of potentially targetable mutations using Archer FusionPlex CTL panel (ArcherDX) did not yield any hits.
Discussion
Each year about 1000 children in Poland are diagnosed with cancer [2], including about 60 cases of the most common kidney tumor – WT [3]. Multimodal therapy including surgery with perioperative CHT and adjuvant RT in high-risk tumors results in 90% 5-year overall survival in localized disease and 75% at the metastatic stage [4].

However, children who underwent RT or CHT are at significantly higher risk of subsequent neoplasms compared to the general population [1, 5, 6]. To decrease the risk of secondary malignancies RT, it is recommended only for high-risk groups, with low total doses and minimal exposure of adjacent organs. In consequence, the incidence rates of secondary malignancies in the subsequent decades have decreased, yet the risk is still higher than in the general population [5].

The cumulative incidence of a secondary malignancy in WT survivors is 0.6% at 10 years, 1.6% at 20 years and 3.8% at 30 years after the initial diagnosis [6]. The most common secondary malignancies include colon cancer (SIR 14.1 95% CI 1.7–51.1), soft tissue sarcoma (SIR 11.4 95% CI 2.4–33.4), liver cancer (SIR 34.7 95% CI 4.2–125.5) and thyroid cancer (SIR 4.4 95% CI 1.2–11.3) [6]. Overall survival for patients with subsequent malignancies is 64.5% at 5 years [6].

In the presented case, the development of the left-sided colon cancer 20 years after initial diagnosis of WT was typical, although the age of 26 years at diagnosis is much below the median age of colon cancer occurrence [2, 5, 6]. Long-term follow-up showed that the surgical resection was curative. However, 45 years after WT treatment the patient developed another neoplasm – leiomyosarcoma of the inferior vena cava. Vascular leiomyosarcomas account for about 2% of adult soft tissue sarcomas, most frequently in 50-60-year-old women [7]. The most common location is inferior vena cava. About 400 cases have been reported in the literature to date, none of which was secondary to the childhood cancer therapy. Due to the rarity of the disease, an optimal treatment has not been established [7].

The presented patient did not receive any adjuvant treatment because of serious postoperative complications. Ovarian cancer diagnosed shortly afterwards as the third subsequent malignancy was typical, regarding the latency period, for radiation-induced solid tumors [5, 6]. This malignancy was treated with standard surgery followed by adjuvant CHT.

Our case is interesting for several reasons. First, despite an increased risk of subsequent neoplasms, childhood cancer survivors seldom develop multiple malignant tumors diagnosed at early stages that can be successfully managed with surgery. Second, the patient was carrying a pathogenic mutation of the NBN gene. Physiologically, the nibrin protein is important in the process of the double-strand breaks DNA repair. The biallelic defects are responsible for the Nijmegen syndrome [8]. Our patient did not present the full spectrum of Nijmegen syndrome features, but multiple malignancies after radiotherapy in childhood are probably connected with the carried mutation. Heterozygotes for NBN mutation are also at increased risk of malignancies [9]. All of the 127 variants of the NBN gene are pathogenic. Finally, it is difficult to define the role of the NBN mutation in the development of subsequent malignancies versus the radio- and chemotherapy in childhood and frequent CT examinations. Recent epidemiological results suggested an increased cancer risk after receiving CT examinations in childhood or adolescence. The carcinogenic role of this factor is unclear due to the possible impact of other cancer predisposing factors. Nonetheless, an Australian study, with a mean follow-up of 9.5 years, reported excess risks of cancer at several sites, and an increase of about 20% in the risk of all cancers, compared with individuals not exposed to CT examination [10].

Conclusion
The presented case exemplifies the importance of genetic counseling in childhood cancer survivors who have not been genetically tested. Wise and watchful follow-up in childhood cancer survivors allows for early diagnosis.

Conflict of interest: none declared

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References
1. Friedman DL, Whitton J, Leisenring W et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the childhood cancer survivor study. J Natl Cancer Inst 2010; 102: 1083–1095.
2. Dzikowska J, Wojciechowska U. Nowotwory złośliwe w Polsce w 2013 roku. Krajowy Rejestr Nowotworów Zakład Epidemiologii, Warszawa 2015.
3. Davidoff AM. Wilms tumor. Adv Pediatr 2012; 59: 247–267.
4. Pritchard-Jones K. Controversies and advances in the management of Wilms’ tumour. Arch Dis Child 2002; 87: 241–244.
5. Turcotte LM, Liu Q, Yasiu Y et al. Temporal trends in treatment and subsequent neoplasm risk among five-year survivors of childhood cancer, 1970–2015. JAMA 2017; 317: 814–824.
6. Lee JS, Padilla B, DuBois SG et al. Second malignant neoplasms among children, adolescents and young adults with Wilms tumor. Pediatr Blood Cancer 2015; 62: 1259–1264.
7. Dalainas I. Vascular smooth muscle tumors: review of the literature. Int J Surg 2008; 6: 157–163.
8. Varon R, Vissinga C, Platzer M et al. Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome. Cell 1998; 93: 467–476.
9. Maraña MJ, Dashi M, Al-Mulla F. Identification of a rare germline NBN gene mutation by whole exome sequencing in a lung-cancer survivor from a large family with various types of cancer. Fam Cancer 2017; 16: 389–394. doi: 10.1007/s10689-016-9954-9.
10. Matthews JD, Forsythe AV, Brady Z et al. Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ 2013; 346: f2360.