Analysis in the Prospective Lynch Syndrome Database identifies sarcoma as part of the Lynch Syndrome tumor spectrum

Dear Editor,

Lynch Syndrome (LS) is the most common hereditary cancer syndrome. It results from heterozygous pathogenic germline variants in the mismatch repair (MMR) genes that are carried by over 1 in 200 individuals. Pathogenic variants in each of the MMR genes, *path_MLH1*, *path_MSH2*, *path_MSH6,* and *path_PMS2,* result in different risks for cancers in organs including the colorectum, endometrium, ovaries, stomach, small bowel, bile duct, pancreas and upper urinary tract [1]. These cancers, but not sarcomas, are commonly cited as LS spectrum cancers. Sarcomas include osteosarcomas (OS) that have a worldwide incidence of 4.3 per million in males and 3.4 per million females per year [2], and soft tissue sarcomas (STS) that are a heterogeneous group of cancers of mesenchymal origin with a population incidence of 3.5 per 100,000 people per year in the US [3]. In the most recent study from the Prospective Lynch Syndrome Database (PLSD) we reported 14 cases of sarcoma among 1808 prospectively observed tumors in 6350 carriers of *path_MMR* variants with 51,646 follow up years (FUY) [1].

The PLSD is an international multi-center prospective observational study without a control group, in which we record cancers diagnosed in genetically confirmed carriers of class 4 and 5 path_MMR variants undergoing long-term surveillance. Data on previous cancers are collected at inclusion.

In the PLSD, the mean age at prospective diagnosis of OS (n=10) was 63 years (range, 32-74) and of STS (n=4) 62 years (range, 57-71). More than half of sarcomas (57%, 8/14) occurred in *path_MSH2* carriers even though they comprised only 40% of PLSD patients, 21% were in *path_MLH1* (3/14), 14% in *path_PMS2* (2/14) and 7% (1/14) in *path_MSH6* carriers. The type of

path_MMR variants identified in OS and STS patients were mainly predicted to cause missense changes (57%, 8/14), followed by deletions (4/14) and predicted splicing changes (2/14). Eight of 14 patients (57%) were male.

Comparing the prospectively observed incidence of OS in the PLSD (21 per 100,000 FUY) to the worldwide general population incidence reported by Mirabello et al. showed a 50–63-fold relative incidence in LS [2]. This is particularly striking as OS is primarily a cancer of childhood and adolescence, while in the PLSD, prospective observation is limited to ages 25–80 years [1]. Cumulative incidence at 75 years (95% confidence interval) was 0.73% (0 – 1.56), 4.24% (0.54-7.93), 0 and 1.57% (0-4.63) in *path_MLH1, path_MSH2, path_MSH6* and *path_PMS2* carriers, respectively, which for *path_MSH2* carriers was significantly higher than the 0.1% population cumulative incidence at 75 years ($p < 0.05$) [3,4]. Lifetime risk of OS in *path_MSH2* carriers based on this comparison would be 42.4-fold (5.4 to 79.3) that of the general population.

In addition to the 14 prospectively observed sarcomas in the PLSD, 16 further patients had been affected by sarcoma before or at their inclusion: 5 with OS and 11 with STS, with mean ages at diagnosis of 48.2 (range, 4-64) and 35.1 (range, 24-54) years, respectively. Again, *path_MSH2* carriers were the most frequently affected (50%, 8/16), followed by *path_MLH1* carriers (38%, 6/16). Regarding the type of *path_MMR* variants identified in these patients, predicted missense changes were most common (7/16), followed by splicing (5/16) and deletion variants (4/16). Regarding gender, equal numbers of females (8) and males (8) were affected.

There is a paucity of studies linking OS and LS, even though MMR deficiency (dMMR) is seen very frequently in OS. In one previous study, loss of expression of MSH2/MSH6 was observed in 81% (54/67) of OS and was associated with better prognosis [5]. By contrast, in another

retrospective study of 304 sarcomas that included only one case of OS, dMMR was confirmed in only 2.3% (7/304), and LS was diagnosed in one of these (14%) [6].

A more recent study found that 6% (45/785) of STS had a microsatellite instability high (MSI-H) or intermediate (MSI-I) signature, and this was concordant with dMMR evaluated by immunohistochemistry. Two of the 45 cases (4.4%) had LS [7]. Most recently, *MSH2* was reported as one of a small number of genes that showed a significantly higher burden of pathogenic or likely pathogenic variants in European OS patients compared to controls (0.4%, 3 of 732 patients) [8].

We conclude that the incidence of OS in LS patients is significantly increased compared to the general population. We suggest that osteosarcoma is part of the LS spectrum in adults and seems to be associated particularly with the *path_MSH2* genotype. The association of STS with *path_MMR* variants is currently less clear, although there are case reports on young LS carriers with soft tissue sarcomas [9,10].

List of abbreviations

dMMR: MMR deficiency

FUY: Follow up years

LS: Lynch syndrome

MMR: Mismatch repair

MSI-H: microsatellite instability high

MSI-I: microsatellite instability intermediate

OS: Osteosarcoma

path_MLH1: Pathogenic (disease-causing) variants of the *MLH1* gene

path_MSH2: Pathogenic (disease-causing) variants of the *MSH2* gene

path_MSH6: Pathogenic (disease-causing) variants of the *MSH6* gene

path_PMS2: Pathogenic (disease-causing) variants of the *PMS2* gene

PLSD: Prospective Lynch Syndrome Database

SFT: Soft tissue sarcoma

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval of the study

The study adhered to the principles set out in the Declaration of Helsinki. It was approved by the Oslo University Hospital ethical committee ref. S-02030 and its data governance rules by the Norwegian Data Inspectorate ref. 2001/2988-2. Genetic testing was performed with informed consent according to local and national requirements and all reporting centers exported only de-identified data to PLSD.

Data accessibility

The cancer risk algorithm is available at the PLSD website (www.plsd.eu) that is based upon the results presented in this report and enables interactive calculation of remaining lifetime risks for cancer in any LS patient by giving their age, gender, and gene variant.

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