Sarcomas in Teachers Using Three-Dimensional Printers: A Report of Three Patients and Literature Review

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Background: While low-cost, small-scale, desktop three-dimensional (3D) printers are gaining popularity in the education sector, some studies have reported harmful emissions of particles and volatile organic compounds during the fused deposition modeling (FDM) process, posing a potential health risk. Sarcomas are rare tumors, constituting a group of diverse rare malignant tumors. While some genetic and environmental factors contribute to the development of sarcomas, most cases are idiopathic and sporadic.

Methods: We secured the medical records and statements about work environment from teachers diagnosed with sarcomas after frequent use of 3D printers in high schools, reviewed the cases, and described them in narrative format. Furthermore, popularization of FDM 3D printers, worrisome emissions released during the printing process, and related precautions and countermeasures were discussed through literature review.

Results: Exceptionally, the cases of sarcomas, such as Ewing’s sarcoma, malignant peripheral nerve sheath tumor, and well-differentiated liposarcoma, arose in a common specific condition. All the teachers regularly operated 3D printers in poorly ventilated spaces for at least 2 years. They had no past or family history of relevant diseases.

Conclusions: We first reported three cases of sarcoma in teachers who used 3D printers in poorly ventilated conditions. Although a relationship between the use of 3D printers and the development of sarcomas has not been determined yet, it is important to come up with measures to protect teachers and students using 3D printers from the potential hazard.

Keywords: Sarcoma, School teachers, Three-dimensional printing, Ultrafine particles, Volatile organic compounds

The expiry of a patent for fused deposition modeling (FDM), one of the additive production technologies, in 2011 ushered in low-cost, small-scale, desktop three-dimensional (3D) printers in the market. This opportunity was especially embraced in the education sector: the education sector accounted for 7.9% of all the 3D printer businesses. During FDM printing, a hard thermoplastic filament is extruded through a heated computer-controlled nozzle, which melts the filament and builds an object in successive layers of plastic on a bed to develop a hard 3D model. Thermal treatment of the thermoplastics changes the physical and chemical features of the filaments, leading to the unwanted emission of particles and volatile organic compounds fumes. These emissions have been reported as a potential health risk, especially in poorly ventilated indoor spaces.

Sarcomas constitute a group of diverse malignant tumors of mesenchymal origin, including more than 70 histologic subtypes. They are rare tumors accounting for...
less than 1% of newly diagnosed malignancies.\textsuperscript{5} In accordance with the Surveillance, Epidemiology, and End Results database, the incidence of soft-tissue sarcoma (STS) is about 3.4 per 100,000 persons.\textsuperscript{6} Bone sarcomas are even rarer, accounting for 0.2% of new cancer diagnoses.\textsuperscript{6} While some genetic and environmental factors are known to contribute to the development of sarcomas, most cases are idiopathic and sporadic, with unknown etiology.\textsuperscript{4}

Unfamiliarly, we came across common characteristics of such a rare disease among teachers who used 3D printers in identical conditions. To the best of our knowledge, such cases have never been reported. Herein, we describe their characteristics and possible association with the use of 3D printers.

\section*{METHODS}

This study was approved by the Catholic University of Korea St. Vincent's Hospital Institutional Review Board (IRB No. VC21ZISI0009). The need for informed consent was waived according to the approved study protocol as this research is a retrospective review and minimal risk one.

We secured the medical records and statements about work environment from teachers diagnosed with sarcomas after frequent use of 3D printers in high schools, reviewed the cases, and described them in narrative format. Furthermore, popularization of FDM 3D printers, worrisome emissions released during the printing process, and related precautions and countermeasures were discussed with a literature review.

\section*{RESULTS}

Patient 1 was a healthy, 30-year-old, high-school teacher in 2014. He used to use a personal 3D printer at home and four different printer brands for various classes and club activities at a school from 2014 to 2016. The teacher moved to another school in 2016 and operated from a separate 3D printing room. The room was approximately $3.3 \times 6.6 \text{ m}^2$ with only a very small ventlight and an entrance door and did not have air purifiers (Fig. 1). There were always at least four printers from four different brands. The two printer models were open type without a high efficiency particulate air (HEPA) filter, and the other two were also not completely sealed without the filter. Therefore, the leakage of emissions could not be prevented. Teachers printed 3D structures at the request of students or taught more than 360 students how to use the printers there. As almost exclusively responsible for 3D printing, the patient stayed and worked for at least 3 hours a day. He spent at least 40 rolls of filaments for a year and simultaneously outputted a huge number of objects there, using all available filaments including soft polylactic acid (PLA), transparent polyethylene terephthalate glycol-based, or acrylonitrile butadiene styrene (ABS)-based filament.

The patient had pain in the right buttock since September 2017. When the symptom worsened, he visited a neurosurgeon and underwent a discectomy in February 2018. Nevertheless, the pain did not improve; therefore, he was immediately referred to a general hospital. A magnetic resonance imaging (MRI) scan detected an $8.3 \times 7.1 \times 6.7 \text{ cm}$ mass with lobulated contour and internal necrotic change in the coccyx, and a positron emission tomography/computed tomography (PET/CT) scan revealed multiple $^{18}$F-fluorodeoxy-glucose-avid lesions. After ultrasound-guided core-needle biopsy for the coccygeal lesion was performed, the patient was transferred to another tertiary hospital because a pathologic examination implied a high-grade sarcoma. Then, the primary lesion was finally confirmed as Ewing's sarcoma based on the immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) results (Fig. 2). Except that his father was treated for thyroid cancer, no relevant factors were revealed in the past or family history. The patient had no problems in lung function or skin condition; however, blood tests revealed abnormal results indicating an inflammatory response such as a white blood cell (WBC) count of 11,340/mm$^3$, 71.1% segmented neutrophil, an erythrocyte sedimentation rate of 132, and anemia.

Fig. 1. Workspace for three-dimensional printing. Patient 1 operated printers in a room of approximately $3.3 \times 6.6 \text{ m}^2$ with only a very small window, an entrance, and no air purifiers.
rate of 26 mm/hr, and 1.08 mg/dL C-reactive protein. Next-generation sequencing by an Oncomine Focus Assay (Thermo Fisher Scientific, Waltham, MA, USA) panel with Ion S5 (Thermo Fisher Scientific) sequencer revealed no meaningful mutations corresponding to tier 1 or 2.

After radiotherapy had been performed on the painful buttock lesion with 40 Gy in 10 fractions, he was administered chemotherapy with alternating vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide cycles for 48 weeks. Four months later, chest, abdomen, and pelvis CT scan revealed an increase in size and number of nodules in both lungs and expansion of the primary lesion with progression of bone destruction. Although the patient then received a cycle of combination therapy with gemcitabine and docetaxel, chemotherapy including etoposide, ifosfamide, and cisplatin for 4 months, and two cycles of irinotecan-tezolozolomide chemotherapy, the disease continued to progress. He eventually expired 2 years and 4 months after the confirmation of sarcoma.

Patient 2 managed 3D printers in a high school and conducted related research since 2017 when he was 31 years old. Ten printers were often used simultaneously in a classroom of 26.2 m², which was sealed by five double windows and an automatic door without a ventilation system or air cleaners. The teacher spent more than 10 hours in the

**Fig. 2.** Patient 1. T1-weighted fast spin-echo coronal (A), fat-suppressed T2-weighted fast spin-echo axial (B), and fat-suppressed contrast-enhanced T1-weighted fast spin-echo sagittal (C) magnetic resonance images of the sacrum showed an enhanced main lesion (arrows) involving the right gluteus maximus, gemelli, ischiococcygeus, and obturator internus, penetrating the right levator ani and puborectalis and infiltrating the perirectal space. Positron emission tomography/computed tomography images revealed ¹⁸⁹F-fluorodeoxy-glucose-avid bone lesions in multiple sites including the left clavicle (D) and right proximal femur (E). Pathology slides of a core-needle biopsy specimen demonstrated a tumorous lesion with necrosis (F), composed of small round cells nests (H&E, × 12.5), and clusters of small round cells (G) with hyperchromatic round to oval nuclei, scant or eosinophilic cytoplasm, and indistinct cytoplasmic membranes (H&E, × 1,000).
room designing and printing. Students would also wait in the classroom while the printers were operating. They mainly used PLA filaments, and in some cases, ABS ones were used. Printers were mostly operated at dawn and night when students were not at school and it smelled a lot of plastic when the door opened in the morning.

The patient had pain in the left buttock and visited an orthopedic clinic in May 2019. An MRI scan of the pelvis revealed an approximately 14.8 × 8.2 × 12.4-cm mass, widening of the first and second sacral foramen, and encasing retroperitoneal neurovascular structures. A $^{99m}$Tc-hydroxymethylene diphosphonate bone scintigraphy of the whole body demonstrated increased radionuclide uptake in multiple regions, compatible with bone metastases. He was referred to a tertiary hospital and a CT-guided core-needle biopsy was performed. Histologically, the lesion was composed of malignant spindle cell. IHC and FISH results were consistent with malignant peripheral nerve sheath tumor (MPNST) (Fig. 3). There were no significant factors of past and family history. The patient did not have any problem with lung or skin condition. Blood tests showed abnormal findings including a WBC count of 14,290/mm$^3$ and 88% segmented neutrophil. Next-generation sequencing by a TruSight Oncology 500 (Illumina, San Diego, CA, USA) panel with NextSeq 550Dx (Illumina) sequencer demonstrated no significant variants corresponding to tier 1 or 2.

Since two cycles of adriamycin-ifosfamide chemotherapy had not showed any response, the chemotherapeutic regimen was changed to a combination of cisplatin, etoposide, and ifosfamide. Although stable disease status was maintained, the treatment was stopped due to adverse effects. Then, the patient was transferred to a cancer center and had proton therapy of 66 Gy in 30 fractions for the lesions in the skull and sacrum. After 7 months, abdomen and pelvis CT scan demonstrated an increase in size of para-aortic lymph nodes, and pazopanib administration was started. As disease progression was identified on PET/CT 6 months later, gemcitabine and docetaxel combination chemotherapy was administered for seven cycles until the regimen was stopped due to adverse effects. Then, he underwent proton therapy for the retroperitoneal lesions. The patient survived 2 years and 9 months after the diagnosis of sarcoma; however, other metastatic lesions were identified again.

In 2015, patient 3 started working at the same school where the patient 1 worked. He was 38 years old. In April, he moved all the 3D printers available in the school at that time into one computer room, which was different from the one used by patient 1. The room was about 13.2 × 6.6 m$^2$ with three small ventlights, two entrances, and no air purifiers. Here, up to four printers were simultaneously operated. The teacher bought 3D printers with one nozzle; however, those were upgraded to a model with two nozzles soon.

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**Fig. 3.** Patient 2. T1-weighted turbo spin-echo sagittal (A), T2-weighted turbo spin-echo axial (B), and contrast-enhanced T1-weighted turbo spin-echo coronal (C) magnetic resonance images of the pelvis showed a large mass (arrows) encasing retroperitoneal neurovascular structures, such as the sacral plexus and iliac vessels, diffusely involving the sacrum. (D) A $^{99m}$Tc-hydroxymethylene diphosphonate bone scintigraphy of the whole body revealed increased radionuclide uptake in the skull, sacrum, and right ischium. (E) A histology slide of a core-needle biopsy specimen (H&E, × 12.5) demonstrated a tumorous condition and a diffuse growth pattern with alternation of high- and less-cellular areas and myxoid stroma. (F) In another slide (H&E, × 1,000), vague tumor cells fascicles with hyperchromatic, oval to elongated nuclei and finely dispersed chromatin, and mild perivascular tumor cell accentuation were identified.
They were open-type printers of a brand without a HEPA filter. After only a roll of PLA filament was consumed, he mainly employed ABC filaments of all available colors because PLA filament was vulnerable to high moisture that it lost its elasticity and broke down when left inside the print. The patient taught or worked at the 3D printer room for more than 2 hours a day. Since 2016, the burden of the printing job was reduced thanks to patient 1. Nevertheless, he used more than 20 rolls of filaments for a year.

In 2017, his right thigh was gradually growing, distinctively different from the contralateral healthy side, and it eventually became impossible to wear ready-made pants. All along, he thought that it was because of extensive exercises. In February 2019, he hurt his right knee from a minor accident and visited a general hospital with knee pain. When a non-enhanced MRI scan was done to check any internal derangement of the knee, a portion of a tumorous lesion was detected. The patient was referred to a musculoskeletal cancer center. A Gadolinium-enhanced MRI scan fully revealed approximately 9.3 × 15.4 × 23.9-cm fatty tumor in the vastus intermedius muscle. Chest, abdomen, and pelvis CT and whole-body PET/CT scans did not show any related lesions. The tumor was suspected to be a well-differentiated liposarcoma and was excised without a biopsy. The lesion was unusually hard and histologically confirmed as the suspected diagnosis (Fig. 4). No relapse was identified for 2 years after surgery. His past or family history did not reveal any relevant abnormality. The patient had no issues in lung or skin condition, and initial blood tests did not reveal any abnormal results indicating inflammatory response. Next-generation sequencing was not performed.

**DISCUSSION**

The innovation of 3D printing revolutionized the industry, with advanced printing technologies further contributing to its growing popularity worldwide. The United States occupies 35.9% of the global 3D printer business, followed by China with 10.6% while South Korea accounts for 3.7%. FDM printers are the most popular choice for schools, libraries, and homes, owing to their affordability, light filament weight, flexibility in processing, and convenience of use. Nonetheless, its printing process generates chemically stable and inert ultrafine particles (UFPs) and volatile organic chemicals (VOCs) regardless of the type of
thermoplastics used.\textsuperscript{7,8} The particles have biopersistence, which favors the inhalation of particles.\textsuperscript{9} In a meta-analysis,\textsuperscript{7,12} descriptive statistics reported that mean 300,980 and 65,482 particles per cm\textsuperscript{3} were released from ABS and PLA filaments, respectively. The particles are largely organic in composition and vary depending on the filaments.\textsuperscript{8} ABS released a greater number of particles compared with PLA, indicating increased exposure to UFPs. Volatile organic compounds such as 1,3-butadiene is classified as carcinogenic to human by the International Agency for Research on Cancer. Styrene and ethylbenzene are also categorized as probably and possibly carcinogenic.\textsuperscript{10} Substantial and characteristic chemical emissions from 3D printers are listed in Table 1.\textsuperscript{10,11} A recent research showed that there will be 4.45 cancerous cases per 10,000 people exposed to 3D printers in a lifetime.\textsuperscript{12}

The use of desktop FDM 3D printers was a common point among the patients in this study. The printing process using thermoplastic filaments is sensitive to changes in ambient temperature; therefore, the windows and doors remained closed and there was no ventilation. It took about 10 minutes for the bed and nozzle to warm up. At this point, if the room air is cold, the melted filaments from the extruder nozzle are not able to adhere securely to the bed. Therefore, they had no choice but to keep watching the process for around 20 minutes in the poorly ventilated room. Then, once the second and third layers were stuck together, the room environment had to be maintained for at least 2 hours, no matter how small the object was, and sometimes for more than 10 hours because the process was still vulnerable to temperature change and the extracted filaments were not yet fused and blew off like noodles.

Ewing sarcoma is the most common in the Caucasi ans and rare in the Asian populations.\textsuperscript{13} It is a highly aggressive malignancy, with a survival rate of 60% to 70% for patients with non-metastatic disease and less than 30% for those with advanced status.\textsuperscript{13} To date, no study has identified environmental risk factors apart from one Australian national study that reported an association between farm exposure and an increased risk of developing Ewing sarcoma.\textsuperscript{14} MPNST is the sixth most common subtype of STS accounting for approximately 5% to 10% of STS cases.\textsuperscript{15} It is generally a high-grade malignancy, with a high probability of local recurrence and distant metastasis; 40% to 65% of patients develop local recurrence and 30% to 60% experience metastasis.\textsuperscript{15} While approximately half of all MPNST sporadically arise, the others are usually observed in patients with neurofibromatosis. Another risk factor is irradiation; 3% to 10% of all the patients have a previous history of radiation exposure.\textsuperscript{15} Liposarcoma is the most common subtype of STS, accounting for around 20% to 25% of all STS.\textsuperscript{4} It can be subcategorized into well-differentiated, dedifferentiated, myxoid/round cell, and pleomorphic liposarcomas.\textsuperscript{4} Well-differentiated liposarcoma is a locally aggressive tumor that has been associated with

\begin{table}[h]
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\caption{Substantial and Characteristic Emissions from Three-Dimensional Printers}
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Emitted substance} & \textbf{Filament} & \textbf{Carcinogenicity (Classification of International Agency for Research on Cancer)} \\
 & \textbf{Acrylonitrile butadiene styrene} & \textbf{Polylactic acid} & \\
\hline
Formaldehyde & + & + & Carcinogenic to humans \\
Acetaldehyde & + & + & Possibly carcinogenic to humans \\
Isovaleraldehyde & + & + & \\
1,3-butadiene & + & & Carcinogenic to humans \\
Ethylbenzene & + & & Possibly carcinogenic to humans \\
Styrene & + & & Probable carcinogenic to humans \\
2,2-butoxyethoxy-ethanol & & + & \\
Chloromethyl methyl sulphide & & + & \\
Propylene glycol & & + & \\
Lactide & & + & \\
Methyl methacrylate & & + & \\
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\end{tabular}
\end{table}
Li-Fraumeni syndrome; however, almost all cases occur sporadically and with unknown etiology. Exceptionally, in the present study, cases of these rare sporadic diseases arose from a common specific environment.

Our present study findings highlight the need for evaluation and caution when using 3D printers in the education sector, considering that not only teachers but also students may be unintentionally exposed to the toxic fumes. So far, it is not clear if persistent exposure to high concentration of emissions released from 3D printers increased the risk of sarcoma development and consequently the mortality rate. Nevertheless, as a measure for reduced exposure, previous studies recommended strictly adhering to the manufacturer’s supplied controls, operating printers in a well-ventilated space and ventilating printers directly, and working away from printers. In addition, if the extruder nozzles are obstructed, the printer should be turned off and ventilated before removal of the cover. The industrial hygiene hierarchy of controls should also be utilized. To produce better results that may enable a critical comparative review of the pertinent literature, researchers in the environmental and occupational medicine should develop standard protocols to assess emissions and perform uniform analysis of each report of FDM 3D printers. Our findings provide a reason for further research to identify a common shared carcinogen in the fume contents and determine the relationship between the use of a 3D printer and development of a sarcoma.

CONFLICT OF INTEREST
No potential conflict of interest relevant to this article was reported.

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