LETTER

A Case of Down Syndrome Who Developed Pancreatic Cancer: A Case Report and Review of Literature

Sneha Purvey[1], Mina Hanna[2], Walid Shaib[2], Muhammad Wasif Saif[1]

[1]Yale University School of Medicine and [2]Hospital of Saint Raphael. New Haven, CT, USA

Dear Sir:

Down syndrome is a frequent form of mental retardation associated with characteristic morphologic features (mongolism) and many somatic abnormalities due to a number of chromosomal aberrations. The characteristic clinical features that discriminate this syndrome from other mental deficiencies were first described by John Langdon Down in 1866 [1]. In 1959, a chromosomal abnormality was proven to cause Down syndrome and most cases found to be associated with trisomy of chromosome 21 except in rare instances of chromosome 21 translocation (4-5%) or mosaicism (2-4%). In the USA, Down syndrome occurs in 1 of every 800 to 1,000 live births or approximately 6,000 infants every year [2].

Down syndrome has been notoriously associated with an increased risk of developing acute leukemia however when it comes to malignant solid tumors, they seem to be globally underrepresented [3]. This may be due to:

i) the increase in mortality from all causes (8-fold increased risk when deaths ascribed to Down syndrome itself were excluded) with not so many individuals with Down syndrome reaching the older ages at which several malignancies tend to occur [2];

ii) Down syndrome patients are sometimes not able to convey their symptoms that would have normally helped direct further investigations and identifying underlying tumors [4].

In addition, the lack of education of their caregivers (especially in a lot of developing countries where parents often feel stigmatized by having a child with Down syndrome) make them less keen seeking medical help for their children and hence underreporting of possible underlying medical conditions including malignancies, thus further contributing to the increase in mortality.

Advances in medicine have helped reducing the mortality of patients with Down syndrome and hence unmasking tumor incidences and their importance as a potential cause of death [3]. Several studies suggest that Down syndrome has a particular tumor profile with some tissues more affected by malignant disease (hematopoietic tissue and germ cells) and others that seem to be protected (central and peripheral nervous tissue, renal tissue and epithelial tissues) [3]. Table 1 shows various sites of malignancies and their incidence in persons with Down syndrome [5].

Table 1. Common sites of malignancies associated with Down syndrome [5].

Site	Standardized incidence rate (95% confidence interval)
Leukemia	17.6 (12.4-24.4)
Acute lymphoblastic leukemia	24.4 (14.9-37.6)
Acute myeloid leukemia	20.3 (10.5-35.4)
Acute unspecified leukemia	26.9 (5.4-78.5)
Leukemia not otherwise specified	1.93 (0.03-10.8)
Lymphoma	
Hodgkin's disease	0.00 (0.00-3.25)
Non-Hodgkin's lymphoma	0.00 (0.00-2.13
All solid tumors	0.50 (0.32-0.75)
Digestive system	0.61 (0.17-1.57)
Stomach	1.10 (0.01-6.14)
Colon	0.89 (0.10-3.23)
Peritoneum	67.8 (0.89-377)
Respiratory system	0.20 (0-1.12)
Lung	0.24 (0-1.32)
Breast	0.00 (0.00-0.41)
Female genital organs	0.70 (0.19-1.80)
Uterus	0.83 (0.01-4.66)
Ovary	1.97 (0.40-5.77)
Male genital organs	1.42 (0.38-3.63)
Testis	1.86 (0.50-4.77)
Urinary tract	1.35 (0.36-3.45)
Kidney	0.84 (0.01-4.66)
Bladder	1.69 (0.34-4.93)
Skin	0.25 (0.03-0.89)
Non-melanoma	0.35 (0.04-1.25)
Eye	3.68 (0.05-20.5)
Brain	0.30 (0.00-1.68)

Received March, 24th, 2010 - Accepted March 31st, 2010

Key words Pancreatic Neoplasms; Down Syndrome; Weight Loss

Correspondence Muhammad Wasif Saif
Yale Cancer Center, Yale University School of Medicine, 333 Cedar Street; FMP 116, New Haven, CT 06520, USA
Phone: +1-203-737-1569; Fax: +1-203-785-3788
E-mail: wasif.saif@yale.edu

URL http://www.serena.unina.it/index.php/jop/article/view/3833/4275

We here report of another patient with Down syndrome who later developed pancreatic cancer.

Our patient is a 42-year-old female with history of Down syndrome who presented with 2 to 3 months history of weight loss up to 9 kg and epigastric abdominal pain. She was given omeprazole (proton pump inhibitor) with minimal relief. Because of her persistent symptoms, a CT of her abdomen and pelvis was performed which revealed enlargement of the pancreatic head, extensive peripancreatic and retroperitoneal adenopathy, intrahepatic and common bile duct dilatation, prominent pancreatic duct, a thin walled 4 cm adnexal cyst, minimal ascites and low density masses in liver, largest measuring 1.7 cm, suspicious of metastasis.

She then underwent CT-guided biopsy of the retroperitoneal lymph nodes that confirmed the diagnosis of moderately to poorly differentiated adenocarcinoma with focal glandular with papillary architecture consistent with metastatic pancreatic adenocarcinoma. These cells were positive for cytokeratin 7, and negative for cytokeratin 20 on immunohistostaining.

After a detailed discussion with the family and consent of the mother and sister, the patient was treated with gemcitabine as a single agent at a dose of 750 mg/m^2 i.v. over 30 minutes increasing to 900 mg/m^2 i.v. and finally to 1,000 mg/m^2 i.v. weekly for 2 out of 3 weeks. This decision was made due to concerns about lack of direct toxicity assessment by the patient. She had a CT scan after 9 weeks which showed stable disease as well as decrease in CA 19-9. Her only toxicities were grade 1 nausea and grade 1 fatigue. A repeat CT scan after 5 months of therapy was performed due to worsening of abdominal pain and elevation of liver enzymes. The radiological findings consisted of decrease in size of both the pancreatic as well as peripancreatic masses but increase in size and number of liver metastases. In addition, a necrotic lymph node in the superior mediastinum was shown to compress the trachea.

Unfortunately the patient developed further elevation of liver function tests and showed worsening of her abdominal pain. A repeat ultrasound showed dilated biliary ducts consistent with common bile duct obstruction. She was therefore admitted to hospital for an endoscopic retrograde cholangiopancreatography. The procedure was attempted but she was unable to withstand the procedure due to significant hypotension and was transferred to intensive care unit with a suspicion of sepsis. The repeat CT scan showed extensive adenopathy with a paratracheal mass causing deviation of trachea to left together with right internal jugular vein dilatation probably due to venous obstruction. There was moderate pericardial effusion, bilateral pleural effusions with bibasilar consolidation in addition to massive ascites and large liver masses.

Radiation oncology and thoracic surgery were consulted and they felt there was no further intervention that could be done to reduce the size of the mediastinal mass which was thought to have metastasized from pancreas.

Based on her co-morbid factors and extensive metastasis of pancreatic cancer, the family decided to withdraw intubation and make her comfortable. She expired shortly after extubation. No autopsy was performed.

Due to the possible association between Down syndrome and pancreatic cancer of our patient discussed above, we searched the literature for the occurrence of digestive tract tumors in patients with Down syndrome. Table 2 lists all benign and malignant gastrointestinal neoplasms reported in Down syndrome patients according to a recent study [4].

The increased lifespan of patients with Down syndrome, the discovery of increased incidence of several solid tumors in them together with the completion of the human genome sequencing efforts has encouraged more research to try and find possible genetic patterns in some solid tumors [3]. Therefore, the importance of establishing a tumor profile for Down syndrome patients lies not only in early detection of such cancers but may also have future repercussions for diagnosis and treatment of these cancers in patients with or without Down syndrome.

With reference to our case, pancreatic cancer was ranked fifth as a cause of cancer death in Down syndrome [6]. The human single-minded 2 (*SIM2*) gene was found to be present in the Down syndrome critical region of chromosome 21. Its short isoform (*SIM2-s)* was detected in pancreatic cancer in addition

Table 2. Benign and malignant digestive neoplasms in Down syndrome.

Organ	Comparison with general population	Neoplasms (No. of patients)	
		Malignant	Benign
Oropharyngeal region	Decrease	4	3
Esophagus	Potential decrease	6	4
Stomach	Potential decrease	17	3
Small intestine	Unclear	1	3
Colon and rectum	Decrease	39	0
Liver (excluding bile ducts)	Potential increase	26	2
Bile ducts(extra and intrahepatic) and gallbladder	Potential increase	6	0
Pancreas	Potential increase	28	1
Total	**-**	**127**	**16**

Table 3. Genes on chromosome 21 potentially involved in Down syndrome digestive tumors.

Tumor site	Gene	Locus	Biological effect
Oncogenes:			
- Esophagus	*ETS2*	21q22.3	Regulation of cell proliferation and differentiation
- Pancreas, colon	*SIM2*	21q22.2	Action on key metabolic enzymes involved in carcinogenesis
Genes possibly protective:			
- Oropharyngeal region	*ANA (BTG3)*	21q11.2-q21.1	Antiproliferative activity
	IFN AR	21q22.1	Receptor of IFN-alpha that suppresses ras-transformation
	TIAM1	21q22.1	Suppression of invasion of epithelial cells
- Stomach	*pS2(TFFI)*	21q22.3	Reduction of proliferative activity by stabilization of mucous gel
- Colon	*ETS2*	21q22.3	Inhibition of ras-transformation

to cancer of the colon and prostate. Interestingly, it was not detected in normal pancreas or colon [4, 7]. Table 3 shows yet other genes on chromosome 21 that are potentially involved in Down syndrome digestive tract tumors.

Such gene mapping is now also being utilized as a potential drug therapy target for solid tumors. Antisense inhibition of *SIM2* expression in a colon cancer cell line caused inhibition of gene expression, growth and eventually led to apoptosis [7]. When administered in nude mice, antisense was found to cause pronounced inhibition of tumor growth with no major toxicity [7].

Finally, we want to re-emphasize the importance of having an awareness of the tumor profile of Down syndrome patients and hence having a higher suspicion index for them. More case reporting should help us gain yet a deeper insight into such a profile.

Conflict of interest The authors have no potential conflicts of interest

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