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CASE REPORT



When a metastatic breast cancer is mimicking a pancreatic cancer: case report and review of the literature

Françoise Derouane^a, Jean-Cyr Yombi^a, Jean-François Baurain^b, Etienne Danse^c, Mina Komuta^d and Halil Yildiz^a

^aDepartment of internal medicine, Cliniques universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; ^bDepartment of oncology, Cliniques universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; ^cDepartment of Radiology, Cliniques universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; ^dDepartment of anatomopathology, Cliniques universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

ABSTRACT

We report the case of a 51 year-old female who complained of jaundice and weight loss. At the time of presentation, she had been in remission from a stage 2a ductal breast carcinoma for 58 months. The clinical presentation was suggestive of a primary pancreas cancer with liver metastases and retroperitoneal lymph nodes. We performed liver and pancreas biopsies that demonstrate a relapse of her old breast carcinoma with positive hormone receptors and HER2 positive.

Conservative treatment by chemotherapy was given with Paclitaxel – Trastuzumab and Pertuzumab. Pancreatic metastases are uncommon. Furthermore, pancreatic metastases from breast cancer are very rare. We performed a review of the literature and found 48 cases of pancreatic metastases from breast cancer.

We would like to highlight by this case that when a pancreatic lesion appears, in patients with a past history of cancer, physicians must not forget the possibility of metastases from primary tumor even if the initial stage, of the tumor, is low. However the diagnosis is not always easy. If liver and pancreatic lesions occur simultaneously, the clinical presentation can mimic metastatic primary pancreatic cancer. Therefore performing biopsy is highly recommended for making the correct diagnosis and also for the staging of the disease and the choice of the best treatment according to immunohistochemical analysis.

KEYWORDS

Breast cancer; pancreatic metastases; ductal carcinoma

Introduction

Metastases to the pancreas from other primary cancer are a rare condition which only occurs in 2% of all the pancreatic malignancies [1,2]. The frequency could be higher since in autopsy series the incidence is reported between 3% and 12% [3]. The primary cancers, which most commonly give rise to metastases to the pancreas are: renal cell carcinoma, lung carcinoma, colorectal cancer, sarcoma, and melanoma [4].

Breast cancer metastases commonly involve bones, liver, and lung but rarely the pancreas [5]. However it appears to be the second primary cancer described in autopsy series of pancreatic malignancies [3].

The treatment of pancreatic metastases, from any primary site, depends on the spreading to other organs at the time of the diagnosis. Even if no guidelines have been established, an isolated pancreatic metastasis may in some cases be removed by surgery with successful outcome, even in breast carcinoma metastasis [2,5,6]. We report here a case of a 51 year-old woman with a past history of ductal breast carcinoma in remission since 58 months, who presented a single head pancreatic lesion and multiple hepatic

lesions, therefore mimicking metastatic primary pancreatic cancer. We also review the literature about pancreatic metastases secondary to breast carcinoma.

Case report

A 51 year-old woman was diagnosed with breast cancer in 2008 without any metastasis. The tumor marker CA15–3 was normal at the time of diagnosis. The treatment consisted of quadrantectomy with lymphadenectomy. Histopathological examination revealed invasive ductal carcinoma classified pT2pN0cM0 consisting of a 3 × 4 × 2.5 cm tumor without any axillary spread (0/8). Immunohistochemical analyses were positive regarding estrogen receptor (ER), progesterone receptor (PR) and Human Epidermal growth Receptor 2 (HER2). Due to its high-risk profile (luminal-B HER 2 positive carcinoma) she was treated with 6 cycles of chemotherapy with Docetaxel and Capecitabine following the protocol-study MINDACT, in association with a HER2 targeted drug (Trastuzumab), the latest one given for a total duration of one year. After chemotherapy, she was treated by radiotherapy and hormonotherapy for a total

duration of 5 years (Letrozole 1 year followed by Goserelin and Tamoxifen for 4 years).

Between 2014 and 2018, she was in complete remission without any complaint. The patient was followed with an annual mammography and blood test. In May 2018, 116 months after the diagnosis, and 58 months after the end of the hormonotherapy, the patient presented for jaundice, epigastric pain, early satiety and loss of weight (10 kg in 1 year). On clinical examination she was icteric. The epigastric region was painful on palpation. Cardiopulmonary examination was normal.

Laboratory tests showed aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels at 192 U/L and 285 U/L, respectively (normal range 13–35 U/L and 7–35 U/L); gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase levels at 1582 U/L and 773 U/L, respectively (normal range <40 U/L and 35–105 U/L); total bilirubin level at 6.8 mg/dL (normal range <1.2 mg/dL) and direct bilirubin level at 6.4 mg/dL, (normal range <0.3 mg/dL). Tumor marker tests showed CA 19–9 level at 0.6 kU/L (normal range <35 kU/L), CEA level at 945 µg/L (normal range <5 µg/L) and CA 15–3 level at 320 kU/L (normal range <35 kU/L). The ultrasound showed a hypoechogenic mass in the head of the pancreas but the margins were irregular and not well-defined (Figure 1(a, b)). At the same time, multiple hepatic lesions were described as well as multiple retroperitoneal pathological lymph nodes. Thoraco-abdominal computed tomography showed an hypoattenuating mass, compressing choledochal duct, in the head of the pancreas (Figure 1(c and d)). Biopsies

of the liver and pancreas lesions were performed by endoscopic ultrasound. Later on, treatment of the choledochal duct stenosis (with a prosthesis) was done after endoscopic retrograde cholangiopancreatography (ERCP).

The histopathological features were compatible with breast carcinoma metastases. Immunohistochemical analyses were positive for cytokeratine-17 (CK17), cytokeratine-19 (CK19), GATA 3, HER2 and negative for cytokeratine-20 (CK20), ER and PR (Figure 2). A chemotherapy regimen with Paclitaxel – Trastuzumab – Pertuzumab was given, following the actual recommendation concerning first-line HER2 positive metastatic disease in previously treated patient. After eight cycles of these treatments, the patient had a stable systemic disease but developed secondary brain metastases with carcinomatosis. Panencephalic radiotherapy was administered and the treatment was pursued with Trastuzumab and Pertuzumab alone. At the time of the publication, the patient is still alive.

Discussion

Breast cancer is the first cancer affecting women. The early detection of this cancer with screening programs permitted to decrease the mortality over the past decade [7]. After initial diagnosis and treatment, these women should be followed for a long period for possible relapse. Recurrences of breast cancer may occur even 20 years after the diagnosis. The follow-up consists at first, in detecting loco-regional relapse with annual mammography. The clinical and biological

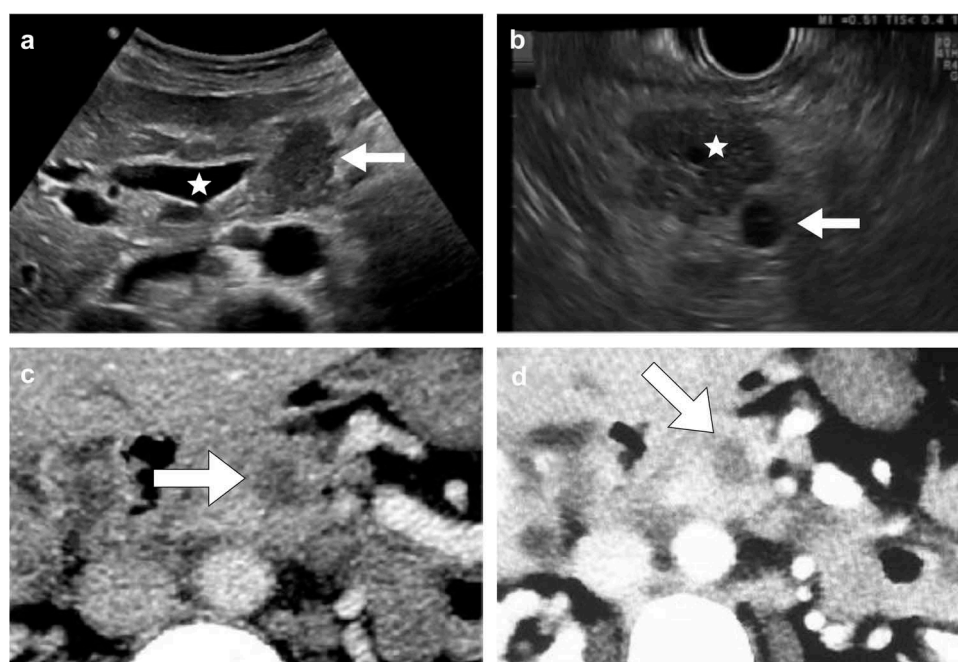


Figure 1. a and b: Hypoechogenic mass in the pancreatic head (asterisk) causing main bile duct dilatation (arrowhead) c: CT post iodine injection at the portal phase acquired on the spectral CT (IQon, Philips Health Care, Cleveland, USA) on the conventional image, an hypoattenuating round mass is visible in the pancreatic head (arrowhead) d: on the low energy reconstructed images (40 keV), the lesion is better delineated (arrowhead).

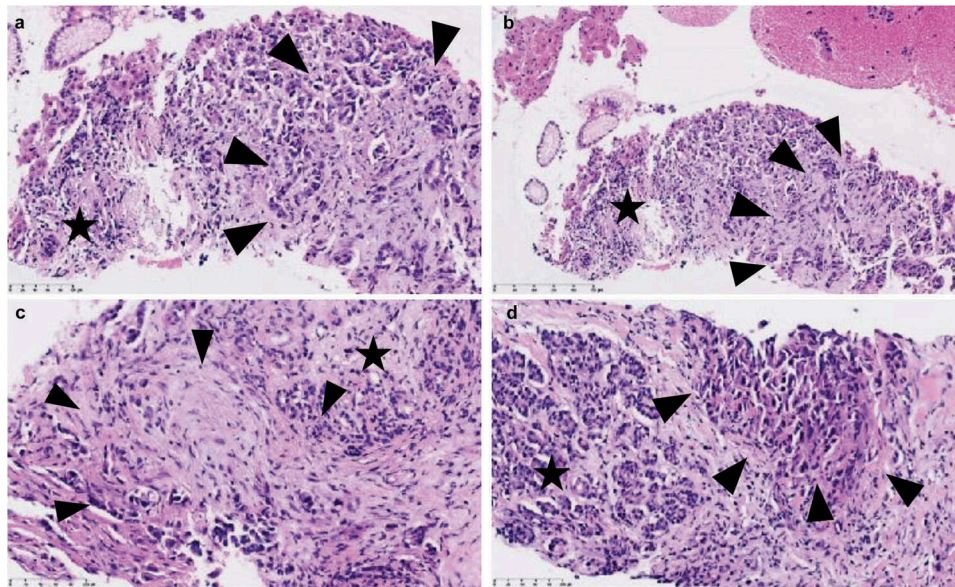


Figure 2. a and b, liver biopsy: Tumor shows irregular glandular structure or solid growth pattern associating with abundant fibrous stroma. Tumoral cells present an eosinophilic cytoplasm with irregular nuclei and dense chromatin. (Hematoxylin and Eosin staining) (arrowhead). c and d, pancreas biopsy: Similar tumor proliferation is seen in the pancreatic parenchyma with fibrotic change. (Hematoxylin and Eosin staining) (arrowhead).

follow-up is essential, and if any abnormalities are detected, complementary imaging should be done. In the case of asymptomatic patients, there is no indication for systematic imaging tests as positive emission tomography (PET), computed tomography (CT) scans, bone scans or brain magnetic resonance imaging (MRI), and also no survival benefit with a systematic dosage of tumor markers [5]. In our case, an annual mammography was performed, considered as normal 2 months before the onset of the abdominal pain.

There are lots of predictive factors for breast cancer metastases such as tumor size, histologic grade, nodal involvement, receptor status or HER 2 status [8]. The link between these factors and the site of the metastases has not been well established but it would appear that patients with ER or PR positive tumor will preferentially have metastases to the bone and patients with HER2 positive tumor or triple negative tumor have a tendency to display visceral metastases to the liver or the brain [8].

Metastases to the gastrointestinal tract or to the pancreas from breast cancer are rare, and most of the time metachronous. The latency period between primary tumor and metastases recurrence may be long, from months to years [1].

In the present case, the HER2 status of the primary tumor explains easily why the patient presented relapse in the liver and later on in the brain. Interestingly, the immunohistochemicals analysis from the pancreatic metastases of our patient, were negative for hormone receptor which may be explained by secondary endocrine resistance, as we may see in tumors previously exposed to endocrine therapy [9], or by the fact that at the moment of the first diagnosis, some tumoral cells were already hormono-resistant and not targeted with the endocrine therapy.

We performed a large review of the literature (MEDLINE database) using PubMed for report concerning metastatic breast cancer in the pancreas between 1982 and 2017 mentioning MeSH terms « breast cancer », « pancreas », « neoplasms metastases ». Articles presenting potentially relevant studies were read and analyzed. We excluded articles in which the characteristics were not relevant and without accurate data.

The review of Apodaca et al. published in 2017 included 29 cases (Table 1) [1] and we found 19 additional cases (Table 2) [6,10–25]. In total we found 48 cases in the literature (Tables 1 and Table 2). The average of disease-free interval, which was described in 48 cases, was 59 months (maximum 348 months.).

It is interesting to note that the head of the pancreas is more affected by the metastases dissemination (84%, $n = 36$, over 43 with the precision) than the tail and appears to be the most symptomatic also. When metastases in the pancreas is symptomatic, it can be misdiagnosed with a primary pancreas cancer because of the non-specificity of the symptoms (jaundice, abdominal pain, gastrointestinal bleeding) [1]. This was the case of our patient. Most of the time, pancreatic metastases, from any primary site, remain asymptomatic and can be accidentally discovered or through routine follow-up. In our review, only seven cases were asymptomatic (7/42, 16.6%) and on these seven cases only one was localized in the head of the pancreas.

Sometimes the origin of the mass is unclear and remains a radiologic challenge for an early recognition of secondary pancreatic tumors [6,22]. The lesions distribution into the pancreas can be classified in

Table 1. Reported cases of pancreatic metastases from the review of Apodaca et al. [1].

	Breast cancer subtype	Disease-free interval (months)	Symptoms	Localization of metastases	Profile of the metastatic disease	Management	Overall survival (months)
Akashi et al. – 2010	Lobular	41	None	Head of pancreas	Solitary	Pancreaticoduodenectomy	28
Apodaca-Rueda et al. – 2017	Ductal	24	Pain	Tail of pancreas	Solitary	Distal pancreatectomy, chemotherapy	18, alive at the publication
Azzarelli et al. – 1982	Lobular	43	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy, radiation therapy	72
Bednar et al. – 2013	Lobular	204	Jaundice, pain	Head of pancreas	Solitary	Pancreaticoduodenectomy	48
Bednar et al. – 2013	Phyllodes	48	Pain	Head of pancreas, lung	Widespread disease	Chemotherapy	15
Bonapasta et al. – 2010	Ductal	24	Jaundice, pain	Head of pancreas	Solitary	Pancreaticoduodenectomy	36
Crippa et al. – 2006	Lobular	60	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy	22
Crippa et al. – 2006	Lobular	36	Jaundice, pain	Head of pancreas	Solitary	Pancreaticoduodenectomy	38
Crippa et al. – 2006	Lobular	84	Jaundice, pain	Head of pancreas	Solitary	Pancreaticoduodenectomy	26
Dar et al. – 2008	Ductal	108	None	Pancreas, liver	Widespread disease	Palliative bypass	6
Engel et al. 1980	Signet-ring cell	46	Pruritus, choloria	Head of pancreas	Solitary	Palliative bypass, chemotherapy	15
Estraviz et al. 2002	Ductal	36	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy	6
Haque et al. 2005	Lobular	168	Jaundice, pain	Head of pancreas	Solitary	Palliative bypass	NA
Kitamura et al. 2003	Ductal	117	Jaundice	Head of pancreas	Solitary	Percutaneous drainage	1
Le Borgne et al. 2000	Lobular	Synchronous	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy, chemotherapy	12
Mehta et al. 1991	Comedo type	36	Jaundice, pruritus	Head of pancreas	Solitary	Pancreaticoduodenectomy, chemotherapy, hormoneotherapy	27
Molino et al. 2014	Lobular	Synchronous	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy, hormoneotherapy	12, alive at the publication
Mountney et al. 1997	Lobular	16	Jaundice, weight loss	Head of pancreas	Solitary	Palliative bypass, hormoneotherapy	24
Moussa et al. 2004	Ductal	132	Acute pancreatitis	Head of pancreas	Solitary	Radiation therapy, chemotherapy, hormoneotherapy	50
Moussa et al. 2004	Lobular	45	Abdominal mass	Body of pancreas	Solitary	Total pancreatectomy, chemotherapy	7
Nomizu et al. 1999	Lobular	80	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy, chemotherapy, hormoneotherapy	18
Odzak et al. 2001	Lobular	Synchronous	Jaundice, ascites	Head of pancreas	Widespread disease	Palliative care	NA
Pan et al. 2012	Lobular	182	Jaundice	Head of pancreas	Solitary	Chemotherapy, hormoneotherapy	21
Pappo et al. 1991	Lobular	24	Jaundice	Pancreas, gallbladder	Widespread disease	Palliative bypass, hormoneotherapy	16
Perez Ochoa et al. 2007	Lobular	1	Jaundice	Head of pancreas, bones	Widespread disease	Biliary stent, pancreaticoduodenectomy, chemotherapy	2
Perez Ochoa et al. 2007	Ductal	108	None	Tail of pancreas	Solitary	Distal pancreatectomy, splenectomy, chemotherapy	2
Razzetta et al. 2011	Lobular	Synchronous	Jaundice, pain, diarrhea	Head of pancreas, bones	Widespread disease	Pancreaticoduodenectomy, neoadjuvant chemotherapy, mastectomy	5
Tohnosu et al. 2006	Scirrhous type	52	None	Tail of pancreas	Solitary	Distal pancreatectomy, chemotherapy, hormoneotherapy	5
Z'graggen et al. 1998	Lobular	96	Jaundice	Head of pancreas	Solitary	Biliary and gastric bypass, chemotherapy	54

NA: not available

Table 2. Main clinical characteristics of patients with breast cancer metastases to the pancreas.

	Breast cancer subtype	Disease-free interval (months)	Symptoms	Localization of metastases	Profile of the metastatic disease	Management	Overall survival (months)
Amir et al. 2018 [9]	Phyllodes	12	Acute pancreatitis	Head and body of pancreas	Solitary	Chemotherapy	12
Cil et al. 2009 [10]	Ductal	12	None	Tail of pancreas	Solitary	Chemotherapy	NA
Jimenez-Heffernan et al. 2006 [11]	Ductal	Synchronous	Jaundice, loss of weight	Pancreas	Solitary	Pancreaticoduodenectomy, chemotherapy	10, alive at the publication
Kliiger et al. 2017 [12]	Ductal	Synchronous	Nausea, diarrhea	Head of pancreas, bones, stomach	Widespread	Chemotherapy	NA
Marrano et al. 2000 [13]	NA	348	NA	Head of pancreas	Solitary	Enucleation	NA
Minni et al. 2004 [14]	NA	312	weight loss, steatorrhea	Head of pancreas (+ new gastric cancer)	Solitary	Enucleation	NA
Mourra et al. 2010 [15]	Ductal	9	NA	NA	NA	Distal pancreatectomy	NA
Mullady et al. 2007 [16]	Lobular	Synchronous	Acute pancreatitis	Head of pancreas	NA	none	0
Nakeeb et al. 1995 [17]	NA	19	NA	NA	NA	Pancreaticoduodenectomy	12
Ogino et al. 2003 [18]	Lobular	72	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy	60
Reddy et al. 2008 [6]	NA	NA	NA	NA	NA	NA	13
Rumancick et al. 1984 [19]	NA	3	NA	Head of pancreas	Solitary	Biliodigestive anastomosis	4
Rumancick et al. 1984 [19]	NA	36	NA	Head of pancreas	Solitary	Biliodigestive anastomosis	30
Serikawa et al. 2012 [20]	Phyllodes	36	Jaundice	Head of pancreas	Solitary	Pancreaticoduodenectomy	NA
Sweeney et al. 2008 [21]	Ductal	60	pain	Head and body of pancreas	Solitary	Distal pancreatectomy, chemotherapy	NA
Tsitouridis et al. 2010 [22]	NA	38	None	Body	Widespread	NA	NA
Tsitouridis et al. 2010 [22]	NA	Synchronous	None	Tail	Solitary	NA	NA
Tunio et al. 2015 [23]	Ductal	Synchronous	Jaundice, pain	Head of pancreas	Solitary	Pancreaticoduodenectomy, chemotherapy	NA
Yu et al. 2000 [24]	Phyllodes	36	NA	Head of pancreas	Solitary	Pancreaticoduodenectomy	NA
Our case (2018)	Ductal	58	Jaundice, pain	Head of pancreas, liver, lung	Widespread	Chemotherapy	Still alive

NA: not available

three categories: small nodules that can lead to a larger mass, a diffuse infiltration of the pancreas or a solitary mass [26]. Among this review, 80% (n = 36, over 45 with the precision) described solitary metastases.

As in our case, differential diagnosis from primary pancreatic adenocarcinoma may be difficult when we observe a dilatation of the main pancreatic duct, because it is quite uncommon with metastases. Although ultrasound (US) and CT may be helpful to differentiate primary pancreatic tumor from metastases, it is not always sufficient and the use of a fine-needle aspiration might be required [3]. Typically, in the US examination, the metastases appear as a solid hypoechogenic mass, with well-defined margins as opposed to a primary adenocarcinoma, which presents irregular margins.

The CT and MRI pattern of pancreatic metastases include the following findings [23,27]: lobulated, well-defined or smooth contours – average size from 1 to 11 cm – usually solid and sometimes cystic – peripheral rim enhancement with a central hypoattenuating necrotic zone – ductal and biliary invasion but no vascular invasion. Recently, as in our case, the detection and the delineation of the pancreatic mass is improved when spectral or dual energy CT systems are used [28]. These systems give access to lower energies images (40 keV) than conventional CT, which helps to a better lesion detection rate. The iodine uptake of the lesion compared to the normal pancreas is also better detected and is measurable.

The treatment of pancreatic metastases depends on different criteria as nature of the primary tumor, widespread disease and the general state of health of the patient. Even if no guidelines have been established, an isolated pancreatic metastases may, in some conditions, be removed by surgery with successful outcome, even in breast carcinoma [2,6]. In our review, 36 cases had surgery treatment, and in these cases, 21 cases benefited from pancreaticoduodenectomy and 6 cases from distal pancreatectomy. In 23 cases, patient underwent chemotherapy or hormonal therapy regimen alone or as adjuvant treatment after pancreatic surgery. The average overall survival (OS), all treatment include, (in the cases where it was described [n = 32]) was 21 months (ranged from 0 to 72 months). Based on this review there was no significant difference in OS if the treatment was surgery alone, chemotherapy or hormonal therapy alone, or a combination of surgery, chemotherapy/hormonal therapy and radiotherapy (OS with surgery alone: 26 months [on the 12 described cases] ranged from 4 to 60 months, OS for combination therapy: 20 months [on the 13 described cases] ranged from 2 to 72 months, OS for chemotherapy alone or hormonal therapy alone: 24 months [on the 4 described cases] ranged from 12 to 50 months).

In conclusion, metachronous pancreatic metastases from breast cancer are rare and when liver and pancreatic lesions occurs simultaneously, it may present as metastatic primary pancreatic cancer. Therefore it is important to take in consideration the clinical history of the patient and to perform biopsies in order to make the correct diagnosis and to administer the best treatment.

Contributing Statement

All authors contributed to the writing of the paper. Dr Derouane Françoise contributed to the paper as first author. All authors have approved the final article

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Françoise Derouane  <http://orcid.org/0000-0002-0199-1366>

Halil Yildiz  <http://orcid.org/0000-0003-3103-1638>

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