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Long Survival and Prolonged Remission after Surgery and Chemotherapy in a Metastatic Mismatch Repair Deficient Pancreatic Neuroendocrine Carcinoma with MLH1/PMS2 Immunodeficiency and Minimal Microsatellite Shift

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Abstract

Pancreatic neuroendocrine carcinomas (NECs) are rare and very aggressive neoplasms with dismal prognosis, especially when metastatic or with negative prognostic factors, such as vascular invasion. To the best of our knowledge, no case of pancreatic NEC with mismatch repair deficiency has been reported to date. We describe a 62-year-old patient who underwent pancreaticoduodenectomy for a NEC located in the pancreatic head, with peri-pancreatic lymph node metastases. Tumor necrosis was prominent and the Ki67 proliferative index was 60%. One year after the diagnosis, the patient experienced recurrence with a left supraclavicular lymph node metastasis, which was surgically removed, followed by standard cisplatin-etoposide chemotherapy.

Neoplastic cells showed combined loss of expression of MLH1 and PMS2 in both primary tumor and lymph node metastasis. Microsatellite instability (MSI) test using a mononucleotide repeats pentaplex PCR (BAT-25, BAT-26, NR-21, NR-22 and NR-24) revealed minimal mononucleotide shifts showing deletion of less than 3 bp at NR-21, BAT-26, NR-24 and NR-22 loci. MLH1 methylation analysis revealed absence of the gene promoter methylation. *BRAF* and *KRAS* mutations were not detected. In gut NECs mismatch repair deficiency phenotype has been reported in about 10% of cases and it represents an independent factor of more favorable outcome. Likewise, our patient is currently alive with a follow-up of more than 12 years after pancreaticoduodenectomy, by itself an unexpected finding for such an aggressive neoplasm.

Keywords: microsatellite instability; minimal microsatellite shift; MLH1; neuroendocrine carcinoma; pancreas; prognosis.

Introduction

Neuroendocrine carcinomas (NECs) of the gastroenteropancreatic (GEP) tract are rare morphologically poorly differentiated neoplasms showing neuroendocrine differentiation [1;3]. NECs should be distinguished from well-differentiated neuroendocrine tumors (NETs), especially from grade 3 NETs, and from other carcinomas, because of their ominous prognosis and different therapeutic approaches [4;5]. Prognostic factors of GEP-NECs include tumor stage (according to ENETS staging system), tumor site (being the foregut origin the better), CD117/c-kit expression, and proliferative activity [6]. In particular, patients with neuroendocrine neoplasm showing a Ki67 proliferative index less than 55% exhibited a more favorable prognosis than those with a Ki67 index greater than 55%, despite lower response rate to therapy. Sahnane et al. demonstrated that the presence of mismatch repair deficiency (MMR-d), causing high level of microsatellite instability (MSI), as well as vascular invasion, are independent prognostic factors in GEP-NECs [7]. However, to our knowledge, no NEC of the pancreas showing MSI has up to now been described. We herein report the first case of a primary pancreatic MMR-d NEC, showing long survival and prolonged remission after metastatic recurrence into a distant lymph node.

Case Report

Clinical history

In April 2007, a pancreatic mass was incidentally found by ultrasonography in a 62-year-old man with HCV-related chronic hepatitis, cryoglobulinemia and a strong smoking history (30 packs-year). Personal or family oncology histories were negative and, in particular, no Lynch syndrome-related cancer was observed. Computed tomography (CT) scan confirmed the presence of a nodule of approximately 3 cm in the pancreatic head with no evidence of distant metastases. A pancreatic biopsy revealed small fragments of poorly differentiated NEC. The patient underwent pancreaticoduodenectomy.

Pathology

The surgical specimen from pancreaticoduodenectomy consisted of a 11-cm segment of duodenum, a 6-cm gallbladder and head of the pancreas measuring 7 x 5 x 3.5 cm. At cut surface, the pancreas showed a yellowish solid mass measuring 3.5 × 3 × 2 cm. The tumor was located 1 cm away from the pancreatic resection margin and was entirely examined.

All slides were reviewed by three neuroendocrine pathologists (AVa, ES, SLR). Histologically, the mass was composed of highly atypical neoplastic cells, with large vesicular nuclei showing prominent nucleoli, high nuclear-to-cytoplasmic ratio, arranged in large and confluent nests (**Fig. 1A and B**), surrounded by some desmoplastic-type stroma. No evidence of glandular or squamous differentiation was seen. Extensive geographic necrosis was present. No evidence of angioinvasion and lymphatic or perineural invasion was found in the plane of sections examined. Mitotic index was 40 mitoses per 2 mm^2. Neoplastic cells invaded peripancreatic soft tissues with a predominantly expansive margin of growth. Metastases in 2 out of 13 peripancreatic lymph nodes were found. Resection margins were negative.

Immunohistochemistry was performed on a Dako Omnis (Glostrup, Denmark) using the antibodies listed in **Table 1**. Immunostainings for pan-cytokeratin 8/18 and synaptophysin were strongly and diffusely positive (**Fig. 1C**), while only focal (<10% of neoplastic cells) cytoplasmic reactivity for chromogranin-A was observed. Immunohistochemistry for trypsin and PD-L1 (CD274) was negative. RB1 nuclear expression was lost in any neoplastic cell, while nuclear p53 immunoreactivity was observed in about 40% of tumor cells. ATRX expression was retained by all neoplastic cells. CD117/c-kit was only focally expressed. The Ki67 proliferative index was 60%. There was a median of 10 (range 5-20) $CD3^+$ intra-tumoral lymphocytes per high-power-field; some peritumoral small lymphoid aggregates were also noted. Neoplastic cells showed loss of immunohistochemical expression of MLH1 (**Fig. 1D**) and PMS2, while retaining MSH2 and MSH6 nuclear positivity.

MSI test was performed using a monomorphic mononucleotide repeats pentaplex, including BAT25, BAT26, NR21, NR22 and NR24 loci. Minimal mononucleotide shifts showing deletion of less than 3 bp at NR-21, BAT-26, NR-24 and

NR-22 loci were identified (**Fig. 3A**). *MLH1* methylation analysis revealed absence of the gene promoter methylation. *BRAF* and *KRAS* mutations were not detected, using the Sequenom MassARRAY system (Diatech Pharmacogenetics, Jesi, Italy).

Morphologic findings, immunophenotype and molecular analysis were consistent with a diagnosis of MMR-d poorly differentiated pancreatic NEC (large cell NEC).

Follow-up

In August 2008 (1 year after the diagnosis), a pathologic left supraclavicular lymph node (2.6 x 1.8 cm) was detected at CT scan and was surgically removed. Histological examination and immunohistochemical stainings, including mismatch repair protein expression, demonstrated a metastasis from the pancreatic NEC (**Fig. 2** and **Fig. 3B**).

Standard chemotherapy with cisplatin-etoposide for 6 cycles was administered. Complete remission on follow-up CT scans was observed since then, and the patient is currently free of recurrence after 124 months (last CT scan, December 2019).

Discussion

Pancreatic NECs, which account for 7.5% of pancreatic neuroendocrine neoplasms, are very aggressive, frequently presenting with lymph node and distant metastases at the time of diagnosis and show a very poor prognosis [2;3;8]. Molecular alterations found in pancreatic NECs are quite similar to those of gut NECs and pivotal drivers include *TP53* and *RB1* mutations [8;9]. Activating *KRAS* gene mutations were identified in 29% of pancreatic NECs by Yachida et al. [9], while *BRAF* mutations seem to be exclusive of colon NECs.

MMR-d has been reported to be extremely rare in pancreatic NETs [8;10], while pancreatic acinar cell carcinomas harbor MMR-d in 14% of cases [11;12]. MMR-d is also a rare event among pancreatic ductal adenocarcinoma, occurring at a frequency of 0.8% in a recent study [13]. Interestingly, all seven MMR-d cancers in that study were found to be associated

with Lynch syndrome and four of the MMR-d patients treated with immune checkpoint blockade had treatment benefit. Rare cases of NETs associated with Lynch syndrome have also been reported [14;15]. Although the personal and family histories for Lynch syndrome-related cancers were negative in our patient, Lynch syndrome could not definitely be excluded, especially in absence of MLH1 methylation and *BRAF* mutation. Therefore, as MMR-d is predictive of Lynch syndrome across a wide spectrum of tumor types, including pancreatic neoplasms, germline genetic assessment should also be considered [16].

In a large Italian series of pancreatic ductal adenocarcinomas, only one (0.3%) showed MSI [17]. This was a medullary type cancer, a rare histological subtype of ductal adenocarcinoma, characterized by poor structural differentiation, syncytial growth pattern, pushing tumor borders, extensive necrosis and, frequently, high density of tumor-infiltrating lymphocytes [18;19]. Medullary cancers may show MMR-d or Epstein-Barr virus infection and may display a more favorable prognosis in comparison with conventional ductal adenocarcinoma. Likewise, the medullary cancer reported by Laghi et al. had MLH1 loss of expression and hypermethylation of hMLH1 gene promoter [17].

Although our case shared some morphologic features and MLH1/PMS2 loss with the medullary subtype, it exhibited a strong and diffuse positivity for the synaptophysin and a more frequently expression chromogranin-A, which supported the final diagnosis of MMR-d NEC.

In our case, the immunohistochemical loss of MLH1 and PMS2 by neoplastic cells was unequivocal in both primary and metastatic tumor tissues. In the light of these results, the electrophoretic pattern obtained with MSI test by pentaplex polymerase chain reaction (PCR) was carefully evaluated in two replicates of both tumor tissues in order to exclude false-negative PCR results. These analyses confirmed the same result revealing an ambiguous MSI profile with only minimal nucleotide contractions of less than 3 bp in four of the five microsatellite loci tested. This phenomenon, known as “minimal microsatellite shift”, has been well described in several solid tumors, especially in non-colorectal (mainly gynecological) cancers [20-22]. In fact, the level of MSI, as detected by PCR, depends on tumor type, e.g. endometrial carcinoma more commonly exhibits short microsatellite alterations in comparison with colorectal cancer [20,21]. Overlooking such minimal microsatellite shifting may lead to a false-negative MSI PCR result and consequently to a wrong classification of an MSI cancer as “microsatellite stable”. In addition, it should also be recalled that the MSI loci

included in the panel we used are colon-specific and may not be as much as sensitive for extra-colorectal cancers, highlighting the need to investigate alternative methods of MSI evaluation, such as testing additional mononucleotide repeat loci, to improve the detection sensitivity by PCR in non-colorectal tumors.

Intratumoral heterogeneity with respect to MMR protein immunohistochemistry has been described in several cancer types, including pancreatic neuroendocrine neoplasms [23]. Nevertheless, the pancreatic NEC described in this study revealed homogeneous loss of nuclear expression of MLH1 and PMS2 in cancer cells, suggesting an early development of MMR-d during carcinogenesis.

MMR-d NECs, often associated with the presence of high number of tumor-infiltrating lymphocytes, have already been described in the tubular gastrointestinal tract, especially in the stomach and colon-rectum [6;7;24;25]. In keeping with our case, they displayed a better prognosis in comparison with non-MSI NEC patients, despite a similar rate of lymph node metastasis and Ki67 proliferative index between the two subgroups. The MMR-d phenotype was identified in 12.4% of GEP-NECs (mainly gastric and colorectal neoplasms) in the study by Sahanane et al. [7], while it was reported in 10% of NECs of the colon-rectum by Cavalcanti et al. [25].

In conclusion, this is the first report of a pancreatic NEC showing MMR-d phenotype. The clinical relevance of our case relies on the favorable outcome, including a long survival, compatible with definitive cure, despite the known poor prognosis of GEP-NECs, especially when metastatic. Based on the literature data and the present case history, we suggest performing immunohistochemistry for mismatch repair proteins in all GEP-NECs to identify the MMR-d cases, which represent a subtype of NECs with better prognosis.

Figure Legend

Figure 1. Pancreatic neuroendocrine carcinoma showing poorly differentiated neoplastic cells (**A**; hematoxylin and eosin). At higher magnification, note the nuclear pleomorphism and the extensive tumor necrosis (**B,** hematoxylin and eosin). Tumor cells show strong and diffuse positivity for synaptophysin (**C**; synaptophysin immunohistochemistry) and

loss of expression of MLH1 (**D**; MLH1 immunohistochemistry). Note, at lower left corner, the internal positive control of stromal and immune cells for MLH1.

Figure 2. The metastasis into the left supraclavicular lymph node showed the same histologic features of its primary tumor depicted in Figure 1. Note, at the lower left corner, the presence of residual lymphoid tissue (**A**; hematoxylin and eosin). Several $CD3^+$ tumor-infiltrating lymphocytes are evident (**B;** CD3 immunohistochemistry). Metastatic cells of neuroendocrine carcinoma showing a high Ki67 labelling index (60%) (**C;** Ki67 immunohistochemistry) and lacking MLH1 expression (**D;** MLH1 immunohistochemistry).

Figure 3. MSI analysis showed the same minimal mononucleotide shifts at NR-21, BAT-26, NR-24 and NR-22 loci in the primary NEC (**A**) and its supraclavicular lymph node metastasis (**B**).

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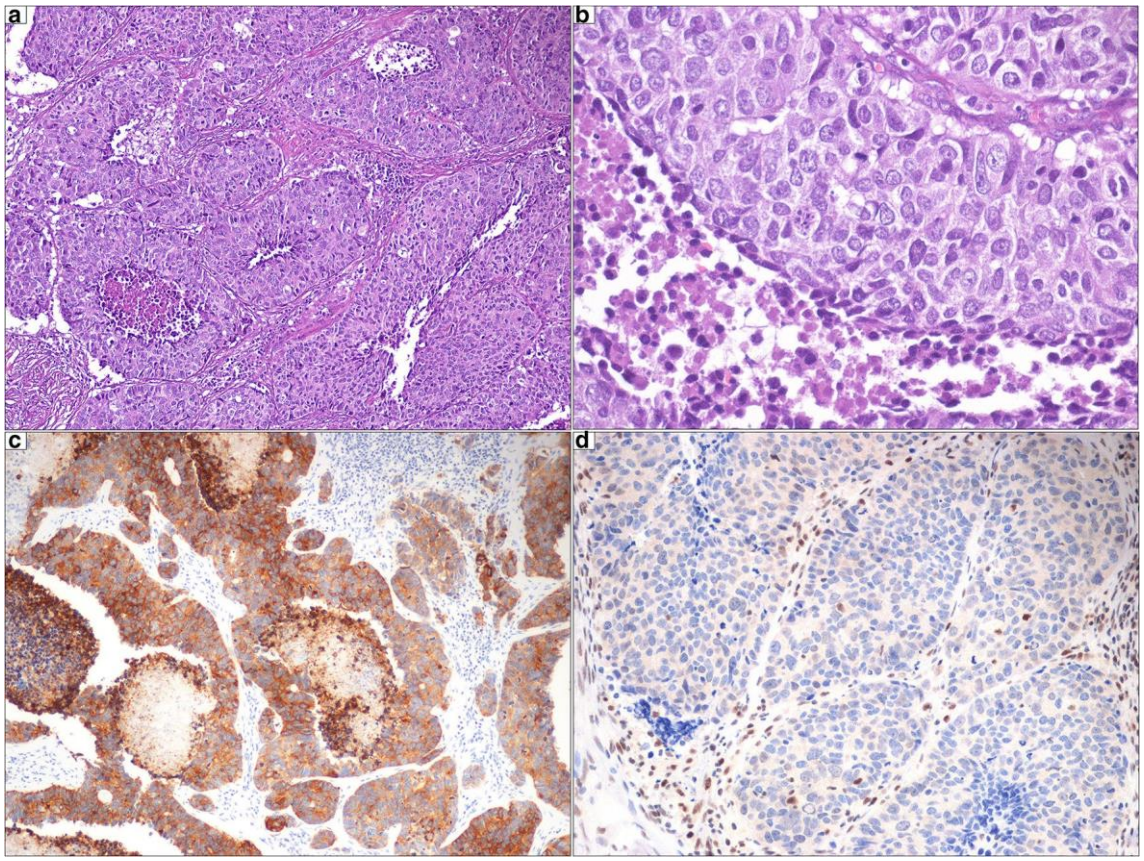
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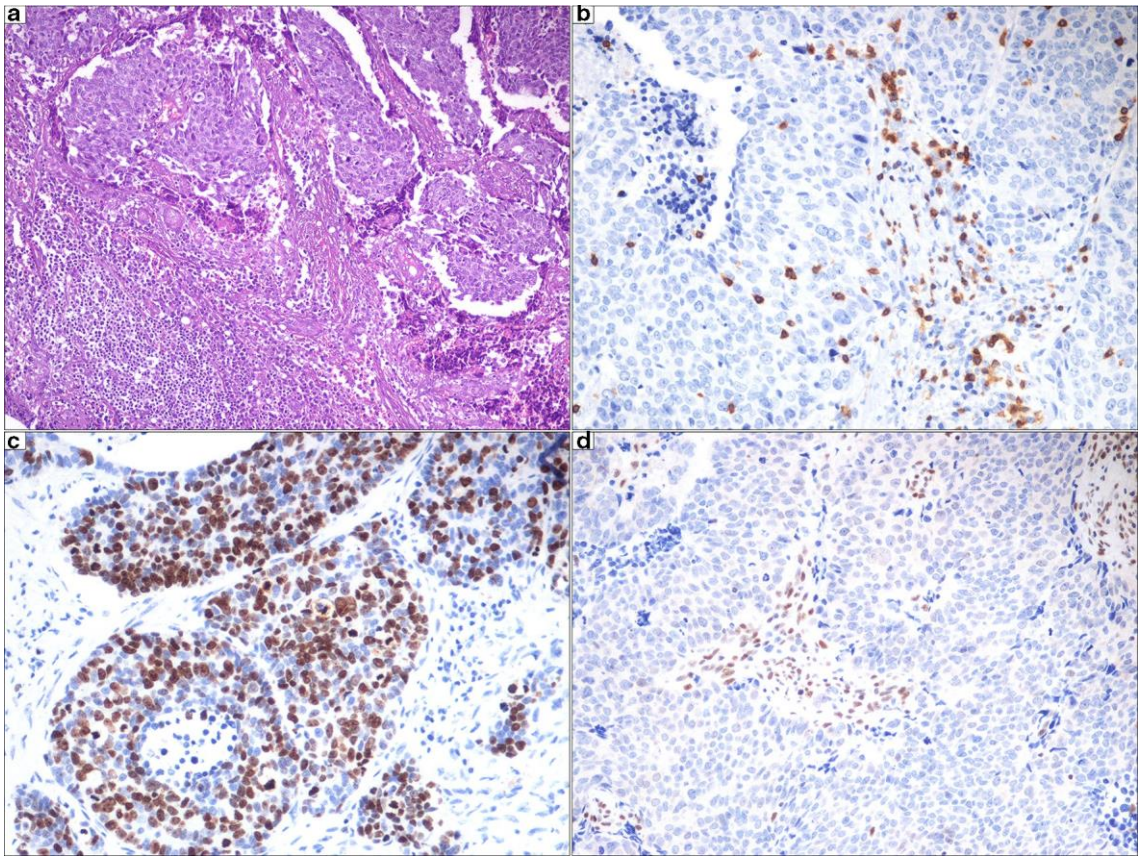
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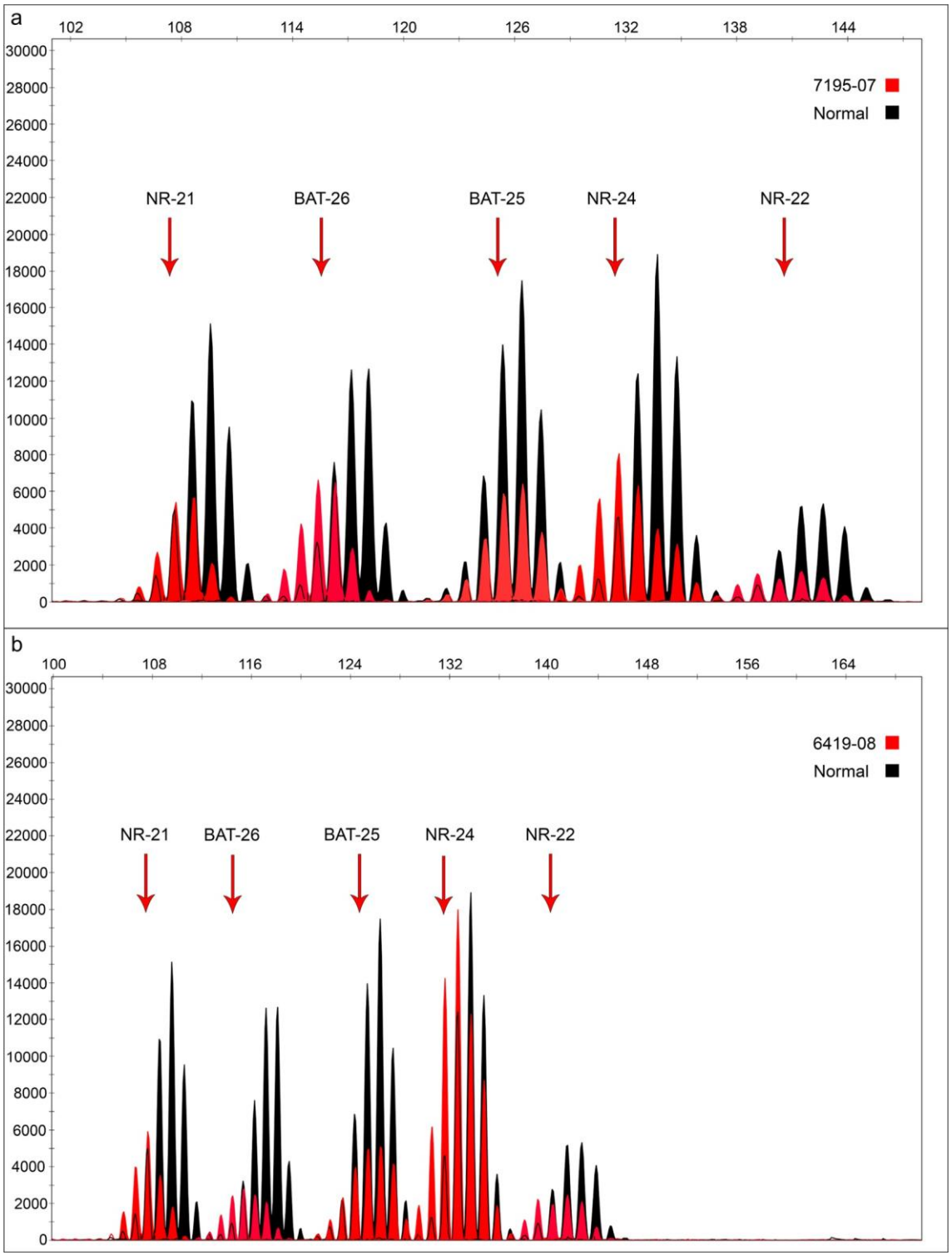
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