Drs. Laszlo Szende and Dr. János Radó: Microangiopathic Haemolysis and Leukoerythroblastosis in Carcinomatosis of Gastric Origin

Case report, review of literature, medical history

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SUMMARY: *Authors refresh and describe a patient suffering from thrombotic microangiopathy induced by gastric cancer who was observed under their care 54 years ago. With the help of literature review they analyse the development of clinical studies and available treatment options during the past half century. This review contains also medical historical issues of the age. The 47-year-old patient who underwent four years earlier a Billroth II. gastric surgery because of a duodenal ulcer disease, was presented with the symptoms of a haematological disorder, haemolytic anaemia, fragmentocytosis, leukoerythroblastosis and thrombopenia. This led to the death of the patient in an unusually short period of time (13 days) with a rapid progression. The clinical picture resembled to that of the seven patients who were observed by the co-author from 1955 till 1962 and who were presented in 1963 at a Haematological Conference held in Pécs, Hungary. The author's tentative clinical diagnosis was metastatic gastric cancer, though there was no conclusive evidence to confirm it. Histology proved the presence of metastatic gastric cancer, though macroscopically no tumour could be found at necropsy. Conclusion is the importance of the hematologic alterations in the detection of hidden metastatic (gastric) cancer. The knowledge of the syndrome of microangiopathic haemolysis, fragmentocytosis, leukoerythroblastosis, thrombopenia associated with metastatic cancer helps to recognize the cause of the disease among the numerous origins of thrombotic microangiopathy. It is suggested that there is a strong relationship between the "big haemolysis" and the tumorous obstruction of the pulmonary arterial tree.*

Keywords: *cancer, metastasis, thrombotic microangiopathy, haemolytic anaemia, leukoerythroblastosis, thrombopenia, Dacie's syndrome*

Abbreviations: MAHA: microangiopathic haemolytic anaemia, TP: thrombocytopenia. LAB: leukoerythroblastosis, DIC: disseminated intravascular coagulation, aHUS: atypical haemolytic uraemic syndrome, HUS: haemolytic uraemic syndrome, CAB: complete androgen blockade, Fr: fragmentocyte, TMA: thrombotic microangiopathy

Microangiopathic haemolysis is a mass destruction of red blood cells in which the resulting anaemia will only be enhanced by transfusion or substitution. It is a severe, rapidly progressing

condition with poor prognosis that often scares not only the patient and relatives, but also the physicians. Red blood cell fragmentation is dominant in the blood film, which is accompanied by myelocytes, promyelocytes and young normoblasts of different age - if complicated by leukoerythroblastosis. This syndrome was summarized and described by Brain, Dacie and Hourihane in 1962 by pointing out that it is often caused by hidden carcinosis. Next year Radó and colleagues reported their own seven gastric carcinoma cases on the 1963 Haematology Days of Pécs, by observing the first case in 1955 as so-called "microangiopathic big haemolyses in carcinomatosis." Presenting our own cases highlighting diagnostic and practical problems and explaining Dacie's approach" (Radó , Takó, Ban and Kelemen 1963). This presentation at Pécs had not been followed by a paper, but a contemporary English language Italian paper (Büchi and Navone 1973) had referred to these cases (by referring the title in Hungarian) and the 12 cases detailed in the book of Endre Kelemen published in England (1974). The rare disease has been dealt with by several other Hungarian publications in 1966, 1970 and 2010 (Szalontay and Horváth 1966; Szöllősy 1970; Deme, Regán, Kalmár et al. 2010).

In this paper we deal with the 8th case in succession which was observed in 1966. The review of fresh literature data associated with this case showed that the description of the case observed 54 years ago can still provide important lessons to be learned. The birth, compilation of this article is quite unusual. The 90-year-old co-author formerly eschewed the description of the case, however, results of literature data collection finally inspired him to take an active part of the compilation of this paper. By recalling the old but still unreported case the co-author (LSz) intended to salute his master on the occasion of the venerable master's 90th birthday.

Background

At the "Haematology Days" conference held in Pécs in 1963 Radó, Takó, Bán and Kelemen described diffuse carcinosis cases of gastric origin where haematological abnormalities were found. Along with the abnormalities referring to haemolytic anaemia, fragmentocytosis and leukoerythroblastosis were also observed. Authors used the concept of microangiopathic haemolysis following the approach of Brain and Dacie by associating the haemolysis to the mechanical harmful effect of tumour cells also present in the vessels; and emphasized the importance of the presence of fragmentocytes in the diagnosis of diffuse carcinomatosis. These haematological abnormalities have been observed during the recent half century owing to numerous reasons, including even non-cancerous ones. Currently the name of *thrombotic microangiopathy (TMA) is used* to determine this haematological syndrome of many possible causes, since their common base is the damage of microcirculation by fibrin-, hyaline and thrombocytic thrombi or/and tumour cell emboli with consequentially resulting endothelial damage.

The main abnormalities that can be observed in thrombotic microangiopathy are microangiopathic haemolytic (Coombs negative) anaemia, presence of fragmentocytes (schistocytes), and thrombocytopenia with consequential ischaemic organ damage (may differ in diverse conditions) and clinical symptoms.

During the past 50 years it has been revealed that thrombotic microangiopathy can be caused by quite numerous factors, some of them not even cancerous. The detailed description of different forms is not intended to be discussed here, however, by mentioning them we also refer

to the most important reviews published in this topic (Prohászka, Szilágyi, Réti et al. 2011; Egészségügyi szakmai irányelv 2017; Arnold, Patriquin and Nazy 2017; Granfortuna 2018; Palma and Sethi 2020; Blasco, Guillén, Quintana et al. 2020). Concerning our case to be presented here *we discuss the forms of cancerous origin*, and we also deal with the associated other paraneoplastic abnormalities, especially with fragmentocytosis and leukoerythroblastosis.

The recall of this old case is reasonable due to the rarity of this syndrome and its diagnostical problems. Owing to the hardships of the currently not hopeless treatment options quite recent publications are also dealing with this matter (Francis, Kalyanam, Terrell et al. 2007; Lee, Otoukesh, Abdi and Nagaraj 2019; Kim and Davidson 2019). We also investigate the reason what could have been the underlying factor of the spectacularly "big haemolysis" in the mentioned cases observed at Pécs, and we also try to provide an overview of the Hungarian medical history concerning this syndrome.

Case report

The 49-year-old male patient has been admitted to the V. Department of Internal Medicine of János Hospital on 12th October 1966. Anamnesis: Patient had duodenal ulcer for 27 years, and 4 years prior to this admission had received a Billroth II gastrectomy. The duodenal ulcer was expansive, already penetrated the pancreas. Following a postoperative period free of complications patient had been well for 4 years. Patient's current complaints: Patient is having nausea for 2 months, with bilious attack like painful episodes following consumption of fatty foods. Three weeks earlier his waist and both legs started to ache along with strong back pain. Two weeks earlier patient fell when drunk and hit his head which keeps aching since then. Cranial X-ray was negative (no fracture). A week earlier when waking up patient felt the right half of his face numb. Patient's faeces are hard, allegedly black. Laboratory test results: erythrocyte sedimentation rate 10 mm/hour, red blood cell count: 3.0 t/l, haemoglobin: 8.4 g/l, white blood cell count. 6.2 g/l, qualitative assessment: 6 myelocytes, 9 metamyelocytes, 19 stabs (band cells), 21 segments, 4 eosinophiles, 1 basophile, 4 monocytes, 36 lymphocytes WBC. 13 normoblasts for 100 WBC, fragmented erythrocytes. Blood films have been examined by the excellent haematologist, Sarolta Hammer, head physician. Based on many years of experience gathered from the samples of similar patients, tumour search had been initiated on the 3rd day of hospitalization. Chest X-ray was normal, bone images showed partly extenuations and partly thickenings. A gastric X-ray had also been done by emphasizing the possibility of the presence of a tumour. This has been done by the excellent radiologist, Dr. György Liszka.

Results: Ablated stomach after Billroth II resection with sound contours. Above the anastomosis the contours of the hind wall are uneven. Primary gastric tumour cannot be observed, but the unevenness of the distal wall of the ablated stomach can be explained possibly with some kind of a retrogastric process (pancreas?). The course of the condition has been dominated by symptoms of haemorrhagic diathesis in the forms of haematemesis, melaena, haemoptoe, epistaxis and dermal bleedings. Thrombocyte count was low but not quantified. Transfusions proved to be ineffective. Definite tumour cannot be found. Patient passed away in 13 days following the presentation of symptoms in deep coma associated with hyperpyrexia, renal failure and hypotension. Though no abnormality referring to a definite tumour has been found, we provided a diagnosis of generalized carcinomatosis of gastric origin.

The necropsy had been expected to be quite interesting, therefore almost all the colleagues were present from the Departments involved. The entire staff of the Department of Internal Medicine, the Head Director of the hospital (Dr. József Takó) and the Department Head of Autopsy, Dr. Antal Kálló and his physicians were present. The autopsy started with an unexpected finding: by opening the cranium, bilateral subdural haemorrhage has been observed in a quantity of around 50 ml, with a significant part of it being liquid. As such, the necessity of official coroner's autopsy has been emerged, but this has been revoked by explaining the subdural haematoma as a consequence of general Haemorrhagic diathesis. The autopsy went on, but no tumour has been found. Focal white thickenings were observed in the spongeous bone mass of the vertebra. The marrow of the femur was yellow and blood-stained. The greyish-white thickened masses were considered as osteomyelosclerosis.

In the stomach, the structure of the gastric-intestinal anastomosis has been seen, and in the upper part of the resection line a lately formed giant lobe has been observed, with supposed ulcers among the lobes The entire mucosa of the stomach had a dark red hue.

The macroscopic findings did not reveal any tumour; however, histological examinations had been initiated (JR). The pathologist leading the autopsy had at first firmly declined this request (by saying that tumours are nowhere to be found), but due to the word of the Head of the hospital samples had been taken for histological assessments. Based on the results of histology the diagnosis of "hidden generalized angiosis cancerosa" has been formed, and under the same title a clinicopathological consultation commenced. Small tumour-emboli have been found in the vessels of several organs ("oncocythaemia was present"), including the pulmonary vessels ("lymphangiosis cancerosa pulmonum"), and a great quantity of these emboli has been found in the giant lobe formed at the location of the gastrectomy. The lesion that seemed to be osteomyelosclerosis earlier proved to be bone marrow cancerosis. This has been so much in the forefront that the pathologist considered the Haemorrhagic diathesis and the anaemia as the consequence of a "penetrative-extruding" bone marrow failure. The origin of the data above is the scientific bulletin of the hospital compiled by Dr. Antal Kálló (Kálló and Radó 1967). The syndrome had been quite novel at that time, and the exact mechanism of the associated clotting abnormality was unknown.

Discussion

This recalled case strengthens the supposition that recognizing and accepting new conditions may require longer period of time. (Slightly, this has been the case in recognising the pararrhythmic effect of antiarrhythmic substances.) *In this case the diagnosis could have been set only due to the firmness of the clinician. This had been founded by the strong certainty in the reasons of the symptoms presented at the conference at Pécs; and recognised in the former seven patients.* The second lesson is the lack of publication of the case. Supposedly the reason for this was that the most important points of the disease had been summarized in the Brain-Dacie article. Publishing the case had also not been motivated by the fact that the treatment of the known cases had been hopeless at that time. One further factor will be mentioned later in the "medical history" section. Retrospectively, these days we can see that those observers were doing right who made their cases published, thus facilitating the description of detailed analysis of the condition and their inclusion in reviews and summaries (Antman, Skarin, Mayer et al. 1979; Lechner and Obermeier 2012; Babu and Bhat 2016; Morton and George 2016; Scully

2016; Weitz 2019). During the past decades many aspects of thrombotic microangiopathy have been entirely explained, and its treatment became possible even in case of cancerous origin. During the recent 50 years it has been revealed that thrombotic microangiopathy can be caused by quite numerous factors, some of them being not even cancerous - this rendered the clarification of the underlying reason more difficult.

The classic form of thrombotic microangiopathy is the thrombotic thrombocytopenic purpura (TTP) and the haemolytic uraemic syndrome (HUS), abbreviated as TTP/HUS due to their common base. TTP is presented with classic pentad symptoms (microangiopathic haemolytic anaemia, fragmentocytosis, thrombocytopenia, fever and central nervous system symptoms). The basic abnormality is the significant drop in ADAMTS13 levels due to congenital or acquired reasons. Its treatment is immediate plasmapheresis. The *haemolytic-uraemic syndrome* is mostly associated with childhood, microangiopathic haemolysis caused by toxic endothelial lesions, thrombocytopenia and renal failure. Most frequently it is caused by the infection of E. coli producing Shiga-toxin (verotoxin) that also causes diarrhoea. In this case plasmapheresis is not the primary treatment option. The *atypical haemolytic-uraemic syndrome* is not caused by Shiga-toxin. In the background of this condition, genetic mutations and complement activation also plays an important role. May be caused by: infections (virus, bacterium, fungus), sepsis, severe hypertonia (eclampsia, HELP syndrome), autoimmune diseases (lupus antiphospholipid syndrome), anti-tumour, immunosuppressive and thrombocyte-aggregating agents, pregnancy, surgery (Prohászka, Szilágyi, Réti et al. 2011; Egészségügyi szakmai irányelv 2017; Arnold, Patriquin and Nazy 2017; Granfortuna 2018; Palma and Sethi 2020; Blasco, Guillén, Quintana et al. 2020).

In the following section we provide an overview of some haematological abnormalities of *cancerous origin*.

Microangiopathic haemolysis in carcinomatosis

In the former case of Pécs and in this current case also the most important abnormalities were the presence of microangiopathic haemolytic anaemia (MAHA), fragmentocytosis, thrombocytopenia and leukoerythroblastosis. Many authors also mention reticulocytosis associated with haemolytic anaemia. *Microangiopathic haemolysis and fragmentocytosis are the most important warning signs for the presence of thrombotic microangiopathy.* This is also shown in the titles of papers concerned with this topic, for example: “microangiopathic haemolysis and thrombocytopenia of cancerous origin”, or “MAHA and carcinoma” or “disseminate carcinomatosis misdiagnosed as TTP”, etc. In today’s practice using automatic blood testing, sometimes only elevated RDW may refer to fragmentocytosis (Ozkalemkas, Ali, Ozkocaman et al. 2005). Fragmentocytosis can also occur without anaemia (Morton and George 2016; Scully 2016; Weitz 2019; Ozkalemkas, Ali, Ozkocaman et al. 2005; DeMarinis, Malik, Matin et al. 2019). The severity of the condition is often indicated by the degree of haemolysis and the lack of effectiveness of transfusions. This happened in this very case and in the case of Pécs, where the title of the presentation already indicated this: “great haemolysis.” (This is the reason why in many publications the authors strived to exclude transfusion incompatibility - just like us in our very first case in 1955, see the section: “medical history”). We’ve also found a severity grading (however, the author was primarily dealing with the aHUS occurring during chemotherapy) where Grade 1 is defined only by the presence of fragmentocytes (less than five

in a field of vision of strong magnification), Grade 2 is defined as elevation of serum creatinine beside increasing number of fragmentocytes, Grade 3 is defined as the further increase of haemolysis and fragmentocytosis, and in Grade 4 the severe elevation of serum creatinine necessitates dialysis treatment by all means (beside transfusion and plasmapheresis), and Grade 5 is the final stage (Blake-Hasdkins, Lechleider and Kreitman 2011).

The elevation of lactate-dehydrogenase (LDH) is also characteristic, but its extent may vary. In TTP it is below 5000 IU but can be higher in case of cancerous origin. The limited diagnostic value of this differentiation is shown by the fact that one of us observed a value of 10,000 IU LDH in a case of anaemia perniciosa.

Thrombocytopenia

Its presence (under 150,000) is obligatory in recognising thrombotic microangiopathy (Szöllősy 1970; Weitz 2019). The occurrence is related to the endothel lesions, therefore it is also present in haemangiomas associated with only local vessel abnormalities (in Kasabach–Merritt-syndrome) (Osman 2019). In case of inorganic devices implanted into the heart or aorta causing the disintegration of only the erythrocytes however, no thrombocytopenia is indicated, even if the haemolysis is severe (Alkhouli, Go, Balla and Berzingi 2019). In the reported case leukoerythroblastosis was quite significant, and this abnormality indicates the penetrative lesion of the bone marrow. This syndrome is known since it was described by Vaughan (Vaughan and Oxon 1936). In cases of TMA of carcinomatous origin it is presented with microangiopathic haemolytic anaemia and thrombocytopenia (Mahdi and Mahdi 2014; Takayashu, Goto, Casagranden et al. 2017; Kotchetkov, El-Maraghi and Narsinghani 2018; Rauch, Al Habeeb and Chang 2011). In these cases the severity of anaemia may vary and sometimes anaemia is not even present (Shamdas, Ahmann, Matzner and Ritchie 1993). Since it can also be detected in case of normal WBC count (in our case as well), automatic blood tests do not cover this phenomenon.

Bone marrow test

In many cases the assessment of the bone marrow facilitates the diagnosis. Thus, for example Lynch, Bakken, Casey and Alfrey (1967) reported in a case very similar to that of our patient's (cause, anamnesis, year of occurrence and course) the tumorous disease had been evidenced in the resected gastric tissue taken 4 years earlier based on the small mucin producing adenocarcinomatic nodule found at the brim of the ulcer. (Another similarity is that autopsy did not reveal any source tumour in that case.) At readmission however, though searching for tumour-like abnormalities but not found any, bone marrow biopsy evidenced the diagnosis of cancer still in vivo.

The assessment of the bone marrow is very important in case of suspecting cancerous disease (Radó, Takó, Bán and Kelemen 1963), *and even in the course of treatment* (Ma, Leckey, Zhang et al. 2019) *for detecting the source of anaemia and thrombocytopenia of unknown origin.*

Haemorrhagic diathesis

In case of thrombotic microangiopathy of cancerous origin, haemorrhagic diathesis is explained partly by the low thrombocyte count and partly by the associated DIC. DIC may occur in itself in case of tumours, therefore it has to be considered.

Involvement of lung vessels

Also, in our case the lung vessels were greatly affected, therefore we started to think that this can play an important role in "great haemolyses." The explanation for this is that since other organs receive only a fraction of stroke volume, each stroke volume is passing through the lung vessels in its entirety. In TMA the most marked phenomenon is the general abnormality of the vessels which is most accented in the lungs. Cancerous TMA often affects pulmonary vessels. In these vessels the tumour emboli, the thrombosis and the initial proliferation raises the pulmonary artery pressure in such an extent that the shearing force on erythrocytes multiplies, further increasing the severity of haemolysis ("great haemolysis"). Thrombotic microangiopathy caused by cancer may take the form of predominantly pulmonary syndrome (pulmonary infiltrate, clinical picture of pulmonary embolism (Gainza, Fernández, Martinez et al. 2014) pulmonary hypertension), in some cases with hemiparesis that may be owing to paradox tumour cell embolism (Morin-Thibault, Wiseman, Fortin et al. 2018). In a case of coronary autopsy, only histology detected the carcinoid origin of the heart's backward failure (Kirsch and Scordi-Bello 2019). (*The author warns his colleagues 54 years after the debate in the morgue that in such cases histology shall be made even if macroscopically no indication is observed.)*

Treatment

The hopeless prognosis in our first case among the patients presented at the Haematology Days at Pécs in 1955 (that was 7 years before the publication of Dacie) was obvious (Radó, Takó, Bán and Kelemen 1963). Based on the results of an extensive statistical survey – among the 168 cases of Lechner and Obermeier (2012) – the prognosis in metastatic gastric carcinoma was much better without MAHA compared to the cases when associated MAHA was also present. For treatment, determining the kind of the tumour causing the syndrome is also very important. This is because more or less improvement can only be expected when applying targeted chemotherapy. Treatment options are increasing with the order of occurrence of the tumour (stomach-breast-prostate).

Prostate cancer is worth to be highlighted. This form of cancer occurs quite frequently, aHUS and DIC are associated with it more frequently compared to other kind of tumours, and it can be treated best (Lechner and Obermeier 2012). Effective treatment can be initiated in some cases even at the level of clinics, this is exemplified by a case from Hungary that is cited in the international literature (Deme, Regán, Kalmár et al. 2010). (A peculiarity of this observation is that organ lesion caused by TMA occurred also on the feet which is considered to be an extremely rare phenomenon [Bibbo and Davis 2005]). Such a report can also be found in literature where oncological treatment of prostate cancer in itself caused thrombotic microangiopathy to cease (Imam, Zahid and Maqbool 2019). It is also worth citing that in the background of what haemophilic symptoms were prostate cancer evidenced: DIC in itself (Duran and Tannock 2006), recurrent nose bleeding, lethal bleeding following pulling of a tooth (Mc Kechnie 1989), and bleeding following basalioma removal (Guldbakke and Schanbacher 2006). The theoretical principles of treating TMA of cancerous origin are highlighted in an earlier work dealing with tumour cell pulmonary embolization, by mentioning that these tumour cells are devastated in the lumen of the vessels without showing parenchymal invasion. Therefore, chemotherapy assist the body in this degradation, and on the other hand it also prevents further embolization (Winterbauer, Elfenbein and Ball 1968).

In order to achieve the earliest initiation of targeted therapy it is worth to overview what signs are indicative of cancerous origin of TMA: 1. Lack of effectiveness of plasmapheresis (in case of TTP improvement can be observed within one or two days). 2. Anamnesis of tumour even if thought to be healed. 3. Presence of DIC (not characteristic to classic TTP). 4. LDH 5 above 5000. Presence of leukoerythroblastosis. 6. Pulmonary symptoms (this is also not characteristic to TTP). 7. TTP is a quickly forming syndrome. In cases of cancerous origin body weight loss, fatigue, back pain last longer (the latter symptom is included by many publications among the clinical signs). 8. ADAMTS (Blasco, Guillén, Quintana et al. 2020) decreases under 10% only in classic TTP (Babu and Bhat 2016; Wynick, Britto, Sawler et al. 2019).

Classic blood film has an important role in recognizing TMA. In the era of automatic blood tests this may be only made for the request of the clinician. Recognizing the syndrome of cancerous TMA facilitates the earliest possible initiation of targeted therapy. Case report can now be found on chemotherapy treatment resulting in shorter or longer remission in cases of TMA associated to gastric, prostate, breast cancers and carcinoses of unknown origin. One of the cases associated with breast carcinoma is quite edifying. This case exemplifies the hardships of both diagnosis and treatment, introduces the progressive hospitalizations included in the Hungarian professional guidelines,[9] and *in this case remission of several months could have been achieved (with doxorubicin and paclitaxel) when half of the erythrocytes in the film were fragmentocytes* (Lee, Otoukesh, Abdi and Nagaraj 2019). The effectiveness of oncology treatments in thrombotic microangiopathy is shown in Table 1 compiled by Tang and Goldstein (2017) based on literature publications of 25 gastric carcinoma cases. Average survival of patients was only 3 months, but 26 months of remission is indicated in the statistics. This is compared to our *Table 1 which has been compiled by us from cases of 9 patients published in literature. These patients suffered not in gastric, but of thrombotic microangiopathy of other carcinoid origin* (Deme, Regán, Kalmár et al. 2021; Lee EH, Otoukesh, Abdi and Nagaraj 2019; Kim and Davidson 2019; Mahdi and Mahdi 2014; Duran and Tannock 2006; Mc Kechnie 1989; Samie, Sandritter and Theilmann 2004; Lin, Chang, Sun and Shih 1995; Fan, Chung-Fan and Wang 2018). Average survival has been 7.85 months. However, we must remark that this is an underestimation, since 4 patients lived somewhat longer than the minimum given, and one patient surviving many months must have been omitted from the statistics, due to lack of exact data. Two patients had remission of a period of more than one year. These are not considered to be quite successful oncology results in neither patient groups, but it is an improvement when compared to the situation 54 years earlier.

Postscript

(János Radó)

The case mentioned in this work was observed by us in 1966. This publication may have been written at least 50 years before and should have been written since then. It did not happen this way, unfortunately. But now - due to the age of the authors - there was time to write it finally. It is quite peculiar that professionally it is still timely, may be considered as up to date. It can be edifying for younger generations of physicians and has some interesting medical history details as well. We cite the very first case among the cases reported at the Haematological Days at Pécs, with which the author met in 1955 - only half a year later that he had been started practicing as a physician. *It has been quite an unusual experience: erythrocyte count was less*

and less following every blood transfusion than before. We thought of some kind of an incompatibility, called in countless potential donors from the family and also outside of the family for in vitro tests, and tried to explore the best fit, but finally we had failed. The patient being a music teacher had an intimate friendship with his professor, Zoltán Kodály, the famous composer, who helped him in gathering the potential donors. Kodály requested István Rusznyák, then professor of the 1st Clinic for Internal Medicine and head of the Hungarian Academy of Sciences. But even for Professor Rusznyák, the syndrome of our patient remained an unrevealed mystery. Sarolta Hammer found in the bone marrow a plethora of myeloblasts, promyelocytes, myelocytes and young normoblasts. Wintrobe mentions this in his Clinical Haematology as Vaughan-like leukoerythroblastosis (Radó, Takó, Bán and Kelemen 1963). Sarolta Hammer has also seen tumour cells in the bone marrow, and she also presented these cells. This group of symptoms then named - though only conditionally and temporarily - as *fragmentocytic haemolysis with carcinomatosis* did not let rest my mind in my further life. From 1955 to 1963 (the time of our presentation at Pécs) I observed 6 further cases of fragmentocytosis and leukoerythroblastosis with "big haemolysis" (Radó, Takó, Bán and Kelemen 1963). Based on the first case, I suspected carcinomatosis in each of the cases. I do not remember exactly for which case we called Endre Kelemen into a consultation. I had the honour to have a friendship with Endre Kelemen (1921-2000) and this was also the case between Endre Kelemen and my superior, József Takó, who had worked together at the Purjesz Clinic at Szeged. Endre Kelemen also had great interest in these mysterious "great haemolysis" cases, where finally the autopsy revealed generalized carcinomatosis, or - as in our case - even autopsy could not find the cause (!) only histology gave us the answer. The disciple of Endre Kelemen, the excellent haematologist Kálmán Rák (1929-2005) often told us that he had become familiar with this haematological syndrome through us. Also, Kálmán Rák has collected cases for our process, and these explain that Endre Kelemen mentions 12 own cases in its book of English publication (Kelemen 1969), the great haematological monography by referring to Radó et al. It is quite surprising that the presentation of Radó, Takó, Bán and Kelemen had been heard at the Haematological Days at Pécs in 1963, and Kelemen also wrote about the topic in his English language book (1969), the work of Endre Kelemen is not mentioned in Dezső Lehoczky's "Retrospect, overview" published in 2017, nor in the Archives of Internal Medicine 2018 Special Edition on Endre Kelemen ("Laudatio of Endre Kelemen"), and nor in the Hungarian Academy of Science's appraisement at 16th May 2019 titled "Endre Kelemen, the legendary medical scientist."

We felt obliged to complement the above appraisement of Endre Kelemen which, however, reflect his works and genius extremely well, but do not mention one of Endre Kelemen's favourite topics that has been detailed in such a meticulous way in his vast monography. The detailed description of Antal Kálló on the pulmonary vessels affected by carcinomatosis morphologically supports the role of altered pulmonary circulation in the occurrence of fragmentocytosis. His vision was well ahead of his time. The entire minutes of the clinicopathological conference has been published by Professor Kálló in the Special Edition of the Scientific reports of János Hospital in the 1967 May-June issue. Professor Kálló (1898–1977) had been one of the greatest personalities of Hungarian pathology. He received the title "Doctor of Medical Sciences" among the first without completing a dissertation. He has made the histological report of his own laryngeal cancer, and learned ventriloquism after laryngectomy, and later even conducted scientific presentations. He has never mentioned, but it was known of him, that his brother was Dean Kálló, whom a street has been named of in the

XII. District of Budapest. In 1944 members of the Arrow Cross Party murdered him for saving the life of Jewish people. The fairest thing should have been to include Dr. Sarolta Hammer, Lead Head Physician of the Central Laboratory of János Hospital, as a co-author in each and every publication of us on microangiopathy. She had been a great expert of haematology. She was the person who directed our attention in 1955 to the blood count and bone marrow abnormalities of our microangiopathic patient. At her former workplace, in the Jewish Hospital, many experts learned the basics of haematology with her guidance. One of us (János Radó) had written many publications with her as a co-author, one of these articles was published in Blood in 1959 (Radó and Hammer). (Since this publication is about myelofibrosis, it is also connected to this work through leukoerythroblastosis). Sarolta Hammer in 1955 (and later as well) considered the publication, report of the new syndrome of microangiopathic haemolysis as too early ("premature"), and as being a laboratory expert, she also held it "too clinical", and thus let me know that she was not inclined to take part in the publication. As a former co-author and colleague of her, I can testify that her unheard-of modesty and unselfishness rather proved to be a hindrance to her publication activities. Who knows what role her reluctance had played in the avoidance of publishing this case report? By all means, the broad haematological knowledge of Sarolta Hammer (1901-1990) had been an extremely important factor in our endeavour of describing this syndrome. These several rows

shall serve as the expression of our gratitude and deepest thanks towards her.

Table 1. Effectiveness of oncologic treatment in tumour-induced thrombotic microangiopathy

Author	Ref. no.	Cancerous disease	Haematologic abnormality	Bone marrow biopsy	Antineoplastic active substance	Effect
Samie	48	unclear	MAHA, TP Fr	positive	cisplatin epirubicin 5-fluorouracil	9 months
Lin	49	unclear	MAHA, TP Fr, LAB	positive	5-fluorouracil mitomycin C cisplatin	summary only dramatic improvement
Mahdi	30	breast	TP, LAB	positive	letrozole denosumab	several months monthly transfusion
Imam	43	prostate	TP, aHUS mild MAHA	touch pos. High PSA	bicalutamide leuprolide docetaxel	>6 months
Kim	16	breast	MAHA+TP Fr		capecitabine	1 year
Lee	15	breast	MAHA+TP Fr		doxorubicin paclitaxel	6 weeks
Fan	50	breast	TP+DIC (no MAHA)	positive	tamoxifen	>6 months
Duran	42	prostate	TP, DIC	positive	bicalutamide leuprolide	>3 months
Deme	7	prostate	aHUS, DIC		TAB	>3 months

Abbreviations: MAHA: microangiopathic haemolytic anaemia, TP: thrombocytopenia LAB: erythroblastosis, DIC: disseminated intravascular coagulation, aHUS: atypical haemolytic uraemic syndrome, TAB: total androgen blockade, Fr: fragmentocyte

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