The „one disease-three clinical stages" achalasia paradigm – equivocal data

To the Editor,

We read with great interest the paper by Surdea-Blaga et al. [1] regarding the clinical and manometric data in achalasia and the current hypothesis of one disease with three clinical stages. Although achalasia is the most studied primary esophageal motor disorder, its etiology is still unknown. The clinical course is longstanding and heterogeneous and predictive factors for treatment response have still not been very well identified.

In our clinic we prospectively analysed a cohort of 98 achalasia patients over a period of 3 years. All patients underwent high-resolution esophageal manometry. The often subtle symptoms, frequently confused with gastroesophageal reflux disease, often result in a substantial delay in diagnosis, in our analysis the average duration to diagnosis being 40 months. Regarding the types of achalasia, type II was the most commonly diagnosed (67%), in accordance to other published data [2]. Type III achalasia appears to be identified with a rare incidence, with only six cases diagnosed in our cohort. We could not identify either gender differences, nor a predilection for a specific age category for the whole cohort at the time of diagnosis.

The comparison between achalasia patients type I and II (type III was not taken into account due to the small number of cases) did not evidence significant differences for gender, age or symptom duration at the time of diagnosis. Regarding symptoms, regurgitation was more common in type II achalasia (p=0.05), whilst a marginal statistical difference (p=0.074) was found for weight loss, still in favor of type II. There were no differences between the two types of achalasia regarding the presence or absence of dysphagia, chest pain, heartburn or nocturnal cough. In a recent study, weight loss seems to be the only symptom that differentiates between the three types, being most frequent in type II (63%) and least frequent in type III (27%), but without being discriminant [3]. Our results are consistent with those of Surdea-Blaga et al. [1], where several studies concluded that on the basis of symptoms, symptom duration or age at diagnosis one can not differentiate between the types of achalasia. Many studies have found that the presence or severity of individual symptoms does not correlate with the manometric findings, degree of esophageal dilatation or prognosis. One study that has to be mentioned dates back to 2003 (before the advent of high-resolution esophageal manometry), in which among the main symptoms of achalasia only regurgitation showed significant correlation with lower esophageal sphincter (LES) relaxation pressure when compared to other individual symptoms [4]. However, when we analyzed the correlation of the Eckardt composite score with the manometric data, we found that the mean Eckardt score was significantly higher in patients with type II achalasia compared to type I (p=0.023).

Comparing the manometric data between the two types of achalasia, we identified higher values of the mean integrated relaxation pressure (IRP) (p=0.012) in type II. No significant differences were identified for the LES resting and relaxation pressures. The lower mean IRP in type I, which corresponds anatomically to a greater esophageal dilatation and possibly a lower pressurization, would support the current paradigm of the different stages of achalasia, with type III being the initial one and type I the final one. Data from the literature also suggest that in advanced stages, mean IRP tends to decrease due to the reduction of esophageal pressurization as well as the progressive destruction of excitatory neurons that counteract the initial effect of the destruction of inhibitory neurons [5].

In conclusion, we also state that the data regarding the new theory of the progression of achalasia from type III to type I are conflicting and more studies are warranted to support this new paradigm.

Ion Bancila, Anca Dimitriu, Cristian Gheorghe
Center of Gastroenterology and Hepatology, Fundeni Clinical Institute, University of Medicine and Pharmacy, Bucharest, Romania

Correspondence: Ion Bancila, ibancila@yahoo.com

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Reply,

To the Editor,

We thank Bancila et al. for their important comments [1]. Their comments emphasize that the data we have so far regarding the progression from one type of achalasia to the other remains contradictory. The „progression" hypothesis states that achalasia is a continuum, starting with type III, followed by type II pattern, with type I pattern as the final stage of the disease, when the esophagus is dilated. A recent study [2] reported histological differences between achalasia subtypes, with more ganglion cell loss in type I achalasia, giving a cellular basis for this hypothesis. In our study [3] we tried to identify clinical and manometric characteristics to support or contradict this idea. Some of our results supported this hypothesis, but others did not. If progression was the case, one would expect type I achalasia patients to be older, with a longer evolution of symptoms and a different pattern of symptoms, such as more regurgitation, heartburn, or cough, given the stasis in the dilated esophagus. As in other studies, including the one of Bancila et al. [1], in our group, patients with type I and type II achalasia were of a similar age, and we did not see a different clinical pattern between achalasia subtypes, nor a longer disease duration in type I compared to type II achalasia. However, more patients with type I achalasia reported that dysphagia worsened in time (patients increased the frequency and the amount of water during meals), compared to type II achalasia patients. In addition, type I patients tended to have a lower body mass index (BMI) compared to type II achalasia patients (p=0.07) [3]. Both these two observations could be related with a longer course of the disease in type I achalasia. We didn't have data about weight loss for our entire cohort, therefore these data were not reported in our study. Data from literature [4] and the results of Bancila et al. [1] showed that weight loss is more likely in type II achalasia. These results cannot be really compared with ours, since the authors did not report in their paper the mean BMI of patients with type I or type II achalasia. Among the manometric parameters, such as Bancila et al. [1], we also reported higher 4s-IRP (integrated relaxation pressure) values in type II achalasia, compared to type I achalasia. In addition, in our cohort, lower esophageal sphincter (LES) resting pressure was significantly higher in type II achalasia [3]. Another study [5] reported higher LES resting pressure values in type II achalasia, but similar IRP values when compared to type I achalasia, possibly due to sampling influence. There is accumulating evidence that with the progression of the disease, there are pressure changes at the level of the LES, but the mechanisms are not completely understood.

In our study, 52.8% of patients had type I achalasia, while type III achalasia was less frequent. The patients with type III achalasia were older [3]. Other studies [5] also reported that type III achalasia was less common, and that patients were older, making less likely the type III pattern as the first stage of the disease. In conclusion, we also believe that so far there are insufficient data to state that achalasia subtypes progress from type III to type I, or even from type II to type I.

Teodora Surdea-Blaga, Liliana David
2nd Medical Department, Emergency County Hospital, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Correspondence: Teodora Surdea-Blaga, dora_blaga@yahoo.com

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Space organization and personnel psychological support: unmet needs in the endoscopic assessment during pandemic

To the Editor,

During the last year, Gastroenterology and Endoscopy Units have been reorganized worldwide in order to contain the SARS-CoV-2 virus spreading [1, 2]. As outlined in a recent manuscript published in the *Journal of Gastrointestinal and Liver Diseases* [3], novel ways of patients' triage have been applied to identify and then perform only strictly necessary endoscopic examinations in location where the first pandemic

wave had hit hardest. Following a better control of the epidemic and the advent of vaccines, such measures have been further reset to improve productivity with the necessary level of safety for both patients and personnel during the "co-habitation" with SARS-CoV-2. This scenario of "dynamic-risk" first led to a renewed and flexible arrangement of the endoscopic spaces and organization into the Endoscopic Units, and it brought a renewed awareness for the needs of and risks to the endoscopic personnel besides those of our patients.

The mental health of the professionals involved in the aforementioned procedures needs to be taken into particular consideration. In fact, in relation to the mental health of professionals working in COVID-19 care units as both first- and second-line staff, symptoms of burn-out (including mental exhaustion, irritability, detachment from reality, and insomnia) are usually expected as correlations of changed daily routines. In a recent survey involving medical and non-medical healthcare workers, Zhang et al [4] reported a higher prevalence of insomnia, anxiety, depressive, somatoform and obsessive-compulsive symptoms in the mental health of the assessed staff. Moreover, the front-line medical staff operating in close contact with infected patients, including gastroenterologists in endoscopic units, displayed a higher score on the measurement of depressive/anxiety symptoms, with a two-fold risk of developing mental health problems [5]. In some cases, the neglected burden on mental health can contribute to a higher risk of burn-out and suicidal behaviour for healthcare professionals. In light of the above, timely and effective interventions including psychological support, psycho-therapeutic, Eye Movement Desensitization and Reprocessing and neuro-feedback interventions should be made accessible to endoscopists involved in first- and second line COVID-19 units.

The half-life of SARS-CoV-2 in aerosol has been estimated at approximately 1.1 hour (95%CI: 0.64–2.64). To prevent the virus transmission, several aspects should be systematically taken into account. Firstly, overcrowding should be always avoided. Crowding is a result of a mismatch among several independent variables related to either the ambient (e.g., walkable surface, room volume) or the occupants (i.e., patients and healthcare personnel). A systematic review commissioned by the WHO and published in 2018 assessed the certainty of the evidence that reducing crowding would decrease the risk of non-TB respiratory disease as moderate-to-high, depending on the disease (https://apps.who.int/iris/bitstream/handle/10665/276001/9789241550376-eng.pdf). Density is an objective measure of crowding and refers to the number of people in any given space - e.g., per square meter. There is no validated threshold for optimal and tolerable crowding index in the endoscopic facilities. Ideally, a value of ≤0.14 person per square meter (corresponding to a 7-square meter surface per person) would allow for a potential inter-personal distance of 3 meters. Notably, crowding depends not only on objective parameters such as the density of people sharing the ambient, but even on the people relationships and mobility (http://condor.stcloud.msus.edu/~jaz/psy373/7.crowding.html).

The air change per hour (ACH) is another pivotal factor affecting the risk of viral transmission. The ACH is the ratio of the volume of air flowing through a space in a certain period of time (the airflow rate) to the volume of that space (the room volume) (https://www.cdc.gov/infectioncontrol/guidelines/environmental/index.html). ACH depends on several factors (air ventilation, free-space volume, room temperature and shape) whose individual contribution drives the design of modern healthcare buildings. According to the WHO guidelines on the Natural Ventilation for Infection Control in Health-Care Settings advised after the SARS outbreak, patients who require airborne isolation precautions should be placed in an "airborne precaution room" with >12 ACH (e.g., equivalent to >80 l/sec. for a 4×2×3m^3 room) and controlled airflow direction. In an airborne precaution room for infection control, a pressure > 2.5 Pa (also 10 Pa) is mechanically maintained relative to the corridor. Negative-pressure endoscopic rooms should be preferred, especially for COVID-19 patients, to abolish the contamination of corridors. Alternatively, well-naturally ventilated rooms may be sufficient only when an adequate time interval between examinations is set. Thirty minutes may be a fair amount of time to decrease the airborne viral load, but this largely depends on windows opening and outdoor conditions (e.g., wind speed, wind exposition).

Gian Eugenio Tontini[1,2], Roberto Penagini[1,2], Maurizio Vecchi[1,2], Bernardo Dell'Osso[5,6,7,] Luca Elli[1,2]

1) Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; 2) Department of Pathophysiology and Organ Transplantation, University of Milano, Milan, Italy; 3) Infectious Diseases Unit, Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; 4) Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy; 5) Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy; 6) Department of Clinical and Biomedical Sciences "Luigi Sacco", University of Milan, Milan, Italy; „Aldo Ravelli" Center for Neurotechnology and Brain Therapeutics, University of Milan, Milan, Italy. CRC Molecular basis of Neuro-Psycho-Geriatrics diseases, University of Milan, Milan, Italy; 7) Department of Psychiatry and Behavioral Sciences, Stanford University, CA, USA

Correspondence: Luca Elli, MD PhD, luca.elli@policlinico.mi.it

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SARS-COV-2 infection might cause transient cutaneous lesions in IBD patients under treatment with adalimumab

To the Editor,

The coronavirus 2019 disease (COVID-19) outbreak, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has shown a wide range of clinical manifestations, including dermatological lesions [1]. Recent data found anti-tumor necrosis factor (TNF) α antibodies less dangerous than expected on the outcome of the inflammatory bowel diseases (IBD) patients with COVID-19, and therefore, their during COVID-19 infection is discouraged [2]. Although the clinical picture may be milder in those patients, some unusual features may be detected.

Case 1

A 48-year-old male was admitted to the Ambulatory of Dermatology due to a 5-day history of fever (max 38°C) associated to maculopapular, painful and itching lesion on the scalp and neck, among hair follicle (Fig. 1). He suffered also from ileal Crohn's disease (CD) and had been under treatment with Adalimumab 40 mg subcutaneously e.o.w. for 10 years without any adverse event. He was under sustained remission for 5 years, and no other comorbidities were reported. He denied any drug intake, excepting paracetamol for fever. Rapid serological qualitative testing and nasopharyngeal swab confirmed SARS-CoV-2 infection. The cutaneous lesions were attributed to SARS-CoV-2: he come back in home to quarantine and started immediately therapy with azithromycin 500 mg/day for ten days. Adalimumab injections were not stopped, and the clinical picture improved rapidly. Fever disappeared within two days, and also dermatological lesions rapidly improved. Pain and itching disappeared within 5 days, and lesions almost disappeared within 10 days. No occurrence of abdominal pain or changes in bowel habits were recorded during the stay home, and also fecal calprotectin assessment was normal (48 mg/kg, normal value <50 mg/kg).

Fig. 1. Cutaneous lesion of the scalp, behind the right ear, occurring together with fever. It appeared red, painful and hitching, and disappeared within 10 days after first occurrence.

Case 2

A 32-year-old male was admitted to the Ambulatory of Dermatology due to a 3-day history of hitching vesicular eruptions, located in the suprapubic region and on the penis. He suffered also from ileo-colonic CD and was under treatment with Adalimumab 40 mg subcutaneously e.o.w. for 3 years without any adverse event. He was under sustained remission for 2 years, and no other comorbidities were reported. He was affected by asymptomatic SARS-CoV-2 infection by 5 days, and cutaneous lesions occurred 2 days after COVID-19 diagnosis. The lesions were attributed to He come back in home to quarantine, and no treatment was prescribed because he was asymptomatic. The cutaneous lesions rapidly improved: itching disappeared within 2 days, and the lesions disappeared within 7 days. Significantly, also in this case no occurrence of abdominal pain or changes in bowel habits were recorded during his stay at home.

Despite their increasing incidence [3], the mechanisms of COVID-19 cutaneous manifestations are not yet well known. It has been postulated an activation of the immune system as a consequence of the infection, while another hypothesis is that the higher angiotensin-converting enzyme 2 expression in skin tissues [4] could be a target for SARS-CoV-2 and explain therefore the cutaneous lesions during COVID-19.

This mechanism could also explain the finding of our cases. Our patients were suffering from CD, under treatment with adalimumab, an anti-TNFα antibody, and were under remission. We can postulate that adalimumab could control significantly the "cytokine storm", without any recurrence of the intestinal disease and just leading to a milder form of the disease (transient cutaneous lesions) when infected by SARS-CoV-2. This hypothesis seems to be confirmed not only by the lower risk of severe complications both in IBD patients [2] and in psoriasis patients under treatment with biologic therapy and suffering from COVID-19 [5].

In conclusion, these cases not only reported an uncommon single manifestation of COVID-19, but also supported further the hypothesis that anti-TNFα antibodies could be of benefit in reducing the risk of severe disease in patients suffering from COVID-19, sometimes causing just transient cutaneous lesions.

Antonio Tursi[1,2], Michele Tiano[3]

1) Territorial Gastroenterology Service, ASL BAT, Andria (BT); 2) Department of Medical and Surgical Sciences, Post-graduate School of Digestive Diseases, Catholic University, Rome; 3) Ambulatory of Dermatology, Sanitary District no. 3, ASL BAT, Andria (BT) - Italy

Correspondence: Antonio Tursi, MD, e-mail: antotursi@tiscali.it

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Diet and lifestyle factors associated with inflammatory bowel disease among Romanian patients: a comparison with a Jordanian cohort

To the Editor,

We read with great interest the article published by Qualqili et al. [1], which presented data from 185 inflammatory bowel disease (IBD) Jordanian patients that completed questionnaires regarding their diet and lifestyle [1]. High-sugar and low-fiber diets are western-associated risk factors associated with the occurrence of IBD and most studies suggest that smoking is a risk factor for Crohn's disease (CD).

In this paper, the percentage of smoking in CD was 54%, whereas in ulcerative colitis (UC) it was 40% and cigarette smoking revealed a significant protective association (OR=0.52; 95%CI: 0.29-0.96) with the risk of IBD, which is an unexpected finding. In IBD, the percentage of fast-food intake per month was higher than in the control group (83% UC; 95.5% CD vs 76% control group). Also, snack consumption was higher in IBD patients: 96% vs 82% of controls consume more than 2 snacks per day.

In terms of incidence and prevalence, Romania has higher rates of IBD when compared to Jordan. In 2004 the incidence in the Romanian population was 0.97 and 0.50/100,000 for UC and CD respectively, whereas the prevalence reached 2.42 and 1.51/100,000 for UC and CD respectively [2]. Epidemiological data from Jordan are scarce, but we know that in this south western country IBD cases are rising and occur among all age groups with a peak incidence in the third decade of life [3].

We recently published a paper on environmental factors in Romanian IBD patients. Similarities between the two cohorts can be observed, even if the number of patients included was smaller. Seventy-six Romanian patients completed the questionnaires (47 with CD and 29 with UC) [4, 5]. Impact of smoking was significant in our CD patients: 35% were active smokers, 22% former smokers, while in UC we found no patient active smoker and 35% were former smokers. 19% of our controls declared that they are active smokers (p<0.001 for the association of smoking with Crohn's disease in our population) [4].

In the Romanian IBD group we found significantly higher consumption of salt (89.5% vs. 52.4%, p <0.001), sweets and sweetened beverages (50% vs.14.30%, p<0.001), processed meat (63.2% vs.28.6%, p<0.001), high fat meat (52.6% vs.19%, p<0.001), fried foods (60.5% vs.4.8%, p<0.001) and chips/nachos/other snacks (23.7 vs. 9.5%, p= 0.08), compared to the control group. Highly salted food was consumed more often by the UC patients than those with CD (85 vs. 62%), significantly increased quantities of sugar are consumed especially by those suffering from UC (47 vs. 38%). High fat meat consumption was more encountered in UC than in CD (55 vs. 51%) and the same was true for fried products consumption (55 vs. 47% vs. 4.8%) and for chips/nachos/other snacks (25 vs. 17%).

Another component of fast food that was studied by us was the bought from shop mayonnaise, and that was consumed daily by 8% of our IBD patients vs. 0% of the control group, and that was statistically significant (p=0.06): 11% in CD and 5% in UC.

Data obtained in these studies reflect significant differences in dietary patterns of people with IBD versus the healthy population. The impact of smoking and other dietary factors is different depending on the population studied (west-European versus east-European versus Asian). However, advice on healthy eating and smoking cessation should be given to all patients with IBD. Larger multinational studies targeting dietary patterns and environmental factors could help identify triggering factors for IBD and optimize patient management.

Carmen Monica Preda[1,2], Raluca Ioana Marin[2], Teodora Manuc[1,2], Andrei Gila[2], Letitia Tugui[2], Mircea Manuc[1,2]

1) Carol Davila University of Medicine and Pharmacy, Bucharest; 2) Gastroenterology & Hepatology Department, Clinic Fundeni Institute, Bucharest, Romania

Correspondence: Carmen Monica Preda, carmenmonica.preda@gmail.com

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What is the world record of alpha-fetoprotein level?

To the Editor,

Alfa-fetoprotein (AFP) has been for many decades the classical biomarker for hepatocellular carcinoma (HCC) [1]. Generally accepted normal values for serum AFP are less than 10ng/mL and values over 500 ng/mL are highly suggestive for HCC [2]. We want to report a case of an extraordinary high level of AFP. To our knowledge this is the highest value of AFP reported in available publications.

A 46-year-old man, with no medical history, was admitted for the appearance of a palpable mass in the right upper quadrant, loss of appetite, nausea, bloating, weight loss (15 kg in 2 months) and fever (37.6^{0}C). Clinical examination revealed asymmetrical abdomen, with a tumoral nodular mass (10/3cm) in the right upper quadrant. The tumor was painful at palpation.

Biological examinations revealed elevated transaminases, cholestasis, hypercholesterolemia, inflammatory syndrome, leukocytosis with neutrophilia. The patient presented positive HBsAg = 1,227.54 ng / ml. To our surprise AFP was very high: 146,493.94 ng/ml, while other tumoral markers: CA 19-9 and CEA were not increased. Checking with the lab, any technical error was excluded.

Abdominal ultrasonography described hepatomegaly, surface nodularity, overall coarse and heterogeneous echotexture with multiple hypoechoic lesions with hyperechoic contour. Contrast enhanced MRI described hepatomegaly, multiple masses of variable attenuation, with maximum size 15 cm, hyperintense signal in T2, hypointense signal in T1 (Fig. 1), with restricted diffusion, hepatic perfusion disorder, intrahepatic biliary dilatation, massive portal vein thrombosis, with periportal infiltration, portal cavernoma, hepatic hilar lymph nodes, ascites.

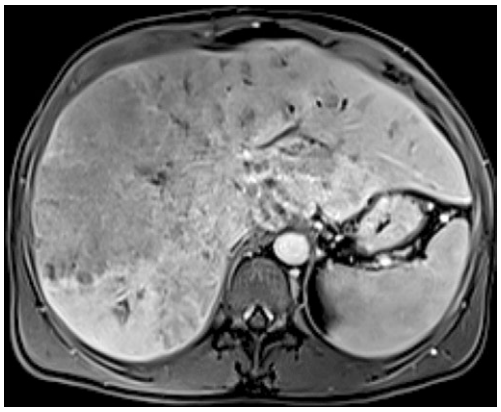

Fig.1. Liver contrast-enhanced MRI showing multicentric HCC.

Correlating the clinical presentation with the imaging report (ultrasound and MRI), and with the laboratory results (very high AFP) we interpreted the case as a multicentric HCC developed on liver cirrhosis, of hepatitis B virus (HBV) etiology. Despite the advanced stage, the patient was scheduled for therapy with sorafenib but died three weeks later.

It is well known that AFP is elevated in HCC [3]. According to literature data, HBV infection is a common etiologic factor for HCC (RR = 15.77), and HBV has also been correlated with more aggressive forms of HCC [3, 4].

Alfa-fetoprotein is a tumor marker commonly used in the early detection of HCC. There is a good correlation between serum AFP level and tumor size [3]. A recent study has attempted to correlate serum AFP level with HCC mortality, concluding that AFP values are not an independent prognostic indicator [5]. It should be noted that in this study, serum average values of AFP were 7,372.9 ng/mL and the median of values was 52.0 ng/mL. In another study, values over 10,000 ng/mL were encountered but none as high as in this case [6].

The AFP value observed in our patient was much higher compared to the average and the median of the values obtained in any other studies, to our knowledge. Therefore, we claim that this patient had probably the highest value of AFP reported in medical literature.

Dalina Diana Pop, Dan Lucian Dumitrascu
2nd Department of Internal Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Correspondence: Dan Lucian Dumitrascu, ddumitrascu@umfcluj.ro

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