Arrhythmogenic Right Ventricular Cardiomyopathy

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In this issue of IMAJ, Belhassen et al. [1] describe an interesting case of a 78 year old patient who experienced multiple episodes of cardiac arrhythmias during a 40 year period. This arrhythmia was finally identified correctly as ventricular tachycardia and not supraventricular tachycardia. The most frequent cause of VT in the elderly is surely related to coronary artery disease. However, after elimination of coronary artery disease, the remaining possible diagnoses were arrhythmogenic right ventricular cardiomyopathy or a healed myocarditis, which had to have been considered before in order for this case to be classified as “idiopathic” VT.

A positive diagnosis of ARVD was suggested by the left bundle branch block electrocardiographic pattern, indicating that VT originated in the right ventricle. However, it is known that VT originating in the left ventricular septum may also exhibit a LBBB pattern [2]. The absence of disease progression during a 40 year period has been observed in my experience but this is not a common feature of ARVD [3].

A surprising positive diagnosis of ARVD was provided by magnetic resonance imaging but was not confirmed by repeated echocardiographic examination. However, MRI did not include gadolinium testing, which would have shown the presence of fibrosis in healed myocarditis or a possible different pattern in the event of ARVD [4].

Myocarditis is a disease with a polymorphic pattern ranging from a transient acute episode with complete healing to the fulminant form leading to hyper-acute heart failure and death in a few days or weeks. The histologic sequel of myocarditis is clusters of adipocytes and fibrosis [4]. In addition, it was recently confirmed that signs of inflammation and possible myocarditis occur more frequently at the time of ventricular arrhythmias in two right ventricular cardiomyopathies, e.g., arrhythmogenic right ventricular dysplasia and the Brugada syndrome [5,6].

In attempting to identify the disease mechanism, genotyping should have been the first step [7]. If positive for a mutation already known in ARVD in which PKP2 is the most frequent, then the title of the authors’ article should be arrhythmogenic right ventricular dysplasia and not arrhythmogenic right ventricular cardiomyopathy, reserving the term ARVC for the wide spectrum of these diseases. Some of them are already known under a different term or will be discovered with the progress of genetics and molecular biology [8,9].

Apart from this discussion on the physiopathogenesis and subsequent terminology of the disease, it is important to emphasize the wise clinical approach of Dr. Belhassen who proposed the two treatment approaches: namely, implantation of a cardioverter defibrillator or anti-arrhythmic drug therapy provided that an electrophysiologic study is performed to ascertain its effectiveness. The latter approach, which was indicated as his preference, was also acknowledged by the patient and eventually proved its effectiveness. The other therapeutic approaches could have been VT ablation using three-dimensional electroanatomic mapping systems [10]. The newest approach could also rely on the interesting dechanneling technique, which requires further investigation [11].

The direction in the future will be to develop new techniques to block progression of the disease, such as the induced Programmed Stem Cells (iPSC) technique, which is able to reproduce the disease-in-the-dish from fibrocytes containing the genetic specific genetic material of each patient [9].

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References

Entamoeba histolytica is the causative agent of amoebiasis, a potentially fatal diarrheal disease in the developing world. The parasite was named “histolytica” for its ability to destroy host tissues, which is probably driven by direct killing of human cells. The mechanism of human cell killing has been unclear, although the accepted model was that the parasites use secreted toxic effectors to kill cells before ingestion. Ralston and colleagues report the discovery that amoebae kill by ingesting distinct pieces of living human cells, resulting in intracellular calcium elevation and eventual cell death. After cell killing, amoebae detach and cease ingestion. Ingestion of human cell fragments is required for cell killing and also contributes to invasion of intestinal tissue. The internalization of fragments of living human cells is reminiscent of trogocytosis (from Greek trogo, nibble) observed between immune cells, but amoebic trogocytosis differs because it results in death. The ingestion of live cell material and the rejection of corpses illuminate a stark contrast to the established model of dead cell clearance in multicellular organisms. These findings change the model for tissue destruction in amoebiasis and suggest an ancient origin of trogocytosis as a form of intercellular exchange.

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Eitan Israeli

Origins of tumor macrophages
To help the immune system fight cancer, it is important to understand the origins and functions of immune cells in tumors and the surrounding tissues. One type of immune cells, macrophages, is present both in tumors and in nearby non-cancerous tissue, but the relationship between these two cell populations is unclear. Franklin and team found that tumor-associated macrophages in mouse mammary differed in form, function, and origin from macrophages found in nearby non-cancerous mammary tissue. Moreover, when they removed macrophages from the tumors but not the other mammary tissue, tumors shrank and cytotoxic T cells – another kind of immune cell that kills tumor cells – infiltrated the tumors. Tumor-associated macrophages may thus be an important therapeutic target.

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Eitan Israeli

Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies
Antibodies capable of neutralizing HIV-1 often target variable regions 1 and 2 (V1V2) of the HIV-1 envelope, but the mechanism of their elicitation has been unclear. Doria-Rose and group have defined the developmental pathway by which such antibodies are generated and acquire the requisite molecular characteristics for neutralization. Twelve somatically related neutralizing antibodies (CAP256-VRC01-12) were isolated from donor CAP256 [from the Centre for the AIDS Programme of Research in South Africa (CAPRISA)]; each antibody contained the protruding tyrosine-sulphated, anionic antigen-binding loop [complementarity-determining region (CDR) H3] characteristic of this category of antibodies. Their unmutated ancestor emerged between weeks 30 and 38 post-infection with a 35-residue CDR H3, and neutralized the virus that superinfected this individual 15 weeks after initial infection. Improved neutralization breadth and potency occurred by week 59 with modest affinity maturation, and was preceded by extensive diversification of the virus population. Human immunodeficiency virus IV-1 V1V2-directed neutralizing antibodies can thus develop relatively rapidly through initial selection of B cells with a long CDR H3, and limited subsequent somatic hypermutation. These data provide important insights relevant to HIV-1 vaccine development.

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Eitan Israeli

Trogocytosis by Entamoeba histolytica contributes to cell killing and tissue invasion
*Entamoeba histolytica* is the causative agent of amoebiasis, a potentially fatal diarrheal disease in the developing world. The parasite was named “histolytica” for its ability to destroy host tissues, which is probably driven by direct killing of human cells. The mechanism of human cell killing has been unclear, although the accepted model was that the parasites use secreted toxic effectors to kill cells before ingestion. Ralston and colleagues report the discovery that amoebae kill by ingesting distinct pieces of living human cells, resulting in intracellular calcium elevation and eventual cell death. After cell killing, amoebae detach and cease ingestion. Ingestion of human cell fragments is required for cell killing and also contributes to invasion of intestinal tissue. The internalization of fragments of living human cells is reminiscent of trogocytosis (from Greek trogo, nibble) observed between immune cells, but amoebic trogocytosis differs because it results in death. The ingestion of live cell material and the rejection of corpses illuminate a stark contrast to the established model of dead cell clearance in multicellular organisms. These findings change the model for tissue destruction in amoebiasis and suggest an ancient origin of trogocytosis as a form of intercellular exchange.

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